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## AZOTEMIA IN TYPHUS FEVER \*

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THE factors which may be responsible for the development of azotemia in severe infectious diseases have been recently reviewed.<sup>1</sup> The diagnosis of azotemia depends upon the biochemical analysis of the patient's blood in a well-equipped laboratory. In typhus fever it is to be expected that under the extremely adverse conditions of hospitalization which are frequently found during epidemics of this disease, azotemia may be unrecognized in many patients. It is, therefore, understandable why comparatively little information on the subject of azotemia is found in the general literature on typhus.

Woodward and Bland in a recent paper<sup>2</sup> called attention to the presence of azotemia in severely ill typhus cases. Azotemia was said to have been universally present in comatose patients. The authors believed that dehydration accounted for azotemia in many of the cases, and stated that adequate fluid replacement often overcame this condition. The presence of other factors such as protein destruction, reduced glomerular filtration resulting from an "unstable circulation," and hepatic dysfunction were believed to account for the development of nitrogen retention in certain cases. Other general descriptions of clinical typhus fever in the English literature which we have been able to review seldom mention the presence of azotemia or its significance.<sup>3, 4, 5, 6, 7, 8</sup>

In 1862 Murchison noted an increase in the blood urea nitrogen in typhus fever.<sup>9</sup> In 1920 Wagner found an elevation of the blood non-protein nitrogen above 100 mg. per 100 c.c. in 15 of 76 typhus cases studied.<sup>10</sup> More recent reports in the German and French literature have discussed the cause of azotemia in typhus.<sup>11, 12, 13, 14, 17</sup>

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There has been no general agreement as to what factors may enter into the genesis of azotemia in typhus. The presence of glomerular nephritis at autopsy has been found as high as 68 per cent in one large series of cases<sup>16</sup> and very rarely in others.<sup>5, 10</sup> Reports on fatal cases with uremia have stated that glomerular nephritis was either absent<sup>14</sup> or minimal.<sup>17</sup> In a recent review article on uremia in typhus it is stated that a "serosal" type of nephritis, the "inflammatory edema of the kidney" of Fahr, may result in nitrogen retention.<sup>14</sup> It has also been said that an "hepato-renal syndrome" may occur, with nitrogen retention and jaundice.<sup>28</sup> The association of hypochloremia and azotemia has been found by some investigators<sup>17</sup> and not by others.<sup>12, 14</sup> Aschenbrenner<sup>14</sup> has recently remarked that uremia in typhus appears to be the result of an increase in protein destruction with a reduction in the excretory ability of the kidneys, brought about by inflammatory or functional changes. However, the author calls attention to the fact that in typhus the diagnosis of glomerular nephritis is extremely difficult to substantiate, and states that only observation over a considerable period of time can confirm the diagnosis. In fatal cases he observes that the microscopic findings in the kidneys are quite variable.

There have been numerous clinical reports on large series of typhus cases studied by German investigators in the past three years, concerning cardiovascular disturbances,<sup>15, 18, 19</sup> the effect of convalescent serum and whole blood,<sup>20, 21, 22</sup> the effect of typhus vaccine on the course of the disease,<sup>23, 24</sup> as well as general clinical discussions of typhus.<sup>25, 26, 27</sup> There are no comments in these papers concerning the presence and incidence of azotemia in typhus, its relation to the severity of the disease, or to the fatality.

It is our belief that the establishment of the presence or absence of azotemia is of interest to the clinician in charge of typhus patients. Its presence not only poses many interesting questions concerning the pathologic physiology of typhus, but, when considered with the clinical picture as a whole, it has been in our experience of considerable aid in indicating desirable measures for supportive treatment. The purpose of this paper is to emphasize the frequency with which nitrogen retention occurs in epidemic typhus, to point out its relation to the severity of the clinical course of the disease, and by the presentation of typical cases of severe or fatal typhus to call attention to certain factors which appear to be of significance in the development of this condition.

*The Background for Reported Observations.* In the two seasons, 1943 and 1944, 159 cases of typhus fever were admitted to the United States of America Typhus Commission ward at the Cairo Fever Hospital.<sup>29</sup> It was possible also to observe numerous cases of typhus fever on the general typhus wards of the hospital. With the exception of three patients, all of the typhus cases studied on the Commission ward were Egyptian males, their ages ranging from 10 to 70 years. By far the greater number of patients were in the 21-35 year age group. These cases were selected either from the

general typhus wards of the hospital or from the receiving ward. In general the attempt was made to study patients as early in the disease as possible. The majority of cases were admitted between the fifth and tenth day of their illness. We were fortunate to obtain a few cases in the first day of the clinical disease, and in four instances to observe patients before the onset of their disease. A comprehensive picture of louse-borne typhus fever, as it occurs in epidemic form, was obtained.

The patients observed on the Commission ward and on the general wards of the Fever Hospital were considered to be suffering from epidemic louse-borne typhus fever. In many instances it was possible to recover rickettsiae from the blood of the patients or from normal lice fed on patients. Every strain thus far isolated has shown the characteristics of louse-borne typhus.<sup>30, 32</sup> In addition, the clinical diagnosis of typhus fever was supported in nearly every instance by the Weil-Felix agglutination reaction or complement fixation tests.<sup>31, 32</sup> Postmortem examination was made in nearly all of the cases which died on the Commission ward. The results of these post-mortem examinations will be reported at a later date.

Many patients admitted to the Commission ward were given various therapeutic agents specifically directed against the disease.<sup>33, 34</sup> A few patients, hospital employees, contracted typhus after vaccination and were studied in the Commission ward. The data from these patients are described elsewhere.<sup>35</sup>

The present paper is restricted entirely to the consideration of the unvaccinated patients who received no special therapy except supportive measures. There were 64 such cases studied on the Commission ward from whom data are available for inclusion in this report. It was possible to obtain additional information on many of these patients on follow-up visits to the Commission ward. These 64 cases are termed "untreated" cases of typhus fever. In addition, data were obtained on 14 patients observed on the general typhus wards of the hospital, who are referred to in this paper as "Cordon" patients.

Early in the course of our observations on typhus fever in Egypt it became apparent that the most severely ill cases showed abnormal concentrations of the blood non-protein nitrogen. In some patients nitrogen retention\* was accompanied by symptoms and signs suggestive of uremia. Factors contributing to the development of azotemia, such as a pronounced hypotension, or severe dehydration, were clearly evident in some cases. A few cases observed in the Commission ward appeared to develop azotemia in the absence of the obvious contributing factors mentioned above. The constancy with which nitrogen retention was present or developed in fatal cases who came under observation in the past two seasons has indicated the high incidence of this condition associated with death from typhus fever.

\* Blood non-protein nitrogen values of 45 mg. per 100 c.c. or higher are interpreted as evidence of nitrogen retention, or azotemia.

*Presentation of Data.* In these studies the concentrations of the blood urea nitrogen and creatinine were determined as well as the concentration of the non-protein nitrogen in many instances. In practically all cases the trend of concentration of the blood urea nitrogen and creatinine was similar to that shown by the non-protein nitrogen. For the sake of simplicity, therefore, the concentration of the blood non-protein nitrogen is discussed throughout this paper.

*Estimation of Severity of Illness.* After discharge from the Commission ward, the severity of the clinical course of the disease was estimated for each patient. The factors which influenced the estimation of severity, and the classification of illness have been described elsewhere.<sup>34</sup> In brief, each patient was classified in one of the following groups:

"B": Cases with minimal symptoms and signs of typhus.

"C": Cases of moderate severity.

"D": Severely ill cases.

"E": Severely ill cases in which fatal outcome was expected at some point in the disease.

"F": Fatal cases.

*The Incidence of Nitrogen Retention and Death in Typhus Fever.* Fifteen of the 64 patients in this study died during the course of the disease, a mortality of 23 per cent (table 1). Thirty-three of the cases (52 per cent) developed nitrogen retention during the disease. The 15 fatal cases were in this group. No deaths occurred in the group of patients who had normal blood non-protein nitrogen concentrations throughout their illness.

TABLE I

The Incidence of Fatal Cases among the Patients \* Who Had Normal Blood Non-Protein Nitrogen Concentrations and the Patients Who Had Nitrogen Retention †

| Year   | Number of Cases | Cases without Nitrogen Retention |        | Cases with Nitrogen Retention |        |
|--------|-----------------|----------------------------------|--------|-------------------------------|--------|
|        |                 | Number                           | Deaths | Number                        | Deaths |
| 1943   | 29              | 14                               | 0      | 15                            | 7      |
| 1944   | 35              | 17                               | 0      | 18                            | 8      |
| Totals | 64              | 31                               | 0      | 33                            | 15     |

\* Unvaccinated "untreated" Egyptian males between 10 and 70 years of age observed on the Commission ward at the Cairo Fever Hospital.

† Values for the blood non-protein nitrogen of 45 mg. per 100 c.c. or higher are regarded as evidence of nitrogen retention.

*The Relation of Nitrogen Retention to the Age of the Patient.* The average age of the 64 patients in this study was 28 years. The average age of the 15 patients who died was 33 years. There were 18 patients in the group of 33 with nitrogen retention who recovered. The average age of these patients was the same as that of the patients with no nitrogen retention (table 2). It is to be noted, therefore, that nitrogen retention was not restricted to the older age group of typhus fever patients.

*The Time of Onset of Nitrogen Retention in Typhus Fever.* In our experience nitrogen retention developed most frequently in the second week of typhus fever. For example, six fatal cases, admitted on the fourth, fifth, and sixth days of illness, had normal blood non-protein nitrogen concentrations on admission and first began to show elevated values between the ninth and eleventh days of illness.

TABLE II

The Incidence of Nitrogen Retention and Death in Relation to Age in Typhus Fever \*

|                 | Cases with No Nitrogen Retention | Cases with Nitrogen Retention |      | Total |
|-----------------|----------------------------------|-------------------------------|------|-------|
|                 |                                  | Recovered                     | Died |       |
| Number of cases | 31                               | 18                            | 15   | 64    |
| Average age     | 27                               | 27                            | 33   | 28    |

\* Footnotes as in table 1.

In a few instances, however, nitrogen retention was encountered in the first week of illness. Three cases in the group of 30 who were admitted before the eighth day had elevated blood non-protein nitrogen concentrations on admission; one was a "D" case, and two were "E" cases. One fatal case whose blood was first examined on the eighth day of illness had a non-protein nitrogen concentration of 96 mg. per 100 c.c. It was very probable that this patient had nitrogen retention before the seventh day of illness.

*Nitrogen Retention and the Severity of Illness.* In 14 cases of moderate severity ("C" 's), four showed nitrogen retention at the time of hospital admission (table 3). These four cases entered the ward in the second week

TABLE III

Comparison of Nitrogen Retention and Severity of Illness \* in 64 Cases of Typhus Fever †

| Classification of Severity | Total Number of Cases in Each Classification | Cases with Nitrogen Retention |  |
|----------------------------|--|-------------------------------|--|
|                            |  | Number in Each Classification | Per Cent of Total in Each Classification |
| "B"                        | 2  | 0                             | 0  |
| "C"                        | 14   | 4                             | 29                                       |
| "D"                        | 26   | 9                             | 35                                       |
| "E"                        | 7  | 5                             | 72                                       |
| "F"                        | 15   | 15                            | 100                                      |

\* The criteria for classification of severity appear in the text.

† Footnotes as in table 1.

of illness. Their blood non-protein nitrogen concentrations fell to normal soon after admission. There was no evidence of oliguria or marked hypotension in these patients.

The severe cases of typhus showed azotemia in greater proportion. Five of the 14 cases with azotemia in groups "D" and "E" developed this condi-

tion while under observation. The others had azotemia at the time of admission.

As may be seen from tables 1 and 3, all of the fatal cases developed azotemia.

*Nitrogen Retention and Blood Pressure in Typhus.* A lowering of the peripheral blood pressure was one of the characteristic features of the disease. With the fall in systolic pressure a decrease in pulse pressure was often present. Abnormal non-protein nitrogen concentrations were frequently noted in cases which had systolic blood pressures below 80 mm. of mercury. A subsequent rise in blood pressure was associated with decreases in the level of the non-protein nitrogen and an increase in the output of urine (chart 4).

A sudden fall in blood pressure from previously observed values was associated with the onset of azotemia in many cases (charts 5, 6, 7, 8). The level to which the blood pressure fell did not appear at times to be as significant as the degree of decline over previous levels. In case No. 5133, for example, a decrease in systolic pressure from 130 mm. to 88 mm. of mercury in 48 hours was associated with a rapid rise in blood non-protein nitrogen. We have frequently observed blood pressures between 80 mm. and 90 mm. of mercury during the acute phase of typhus, however, with no rise in non-protein nitrogen or decrease in urine volume.

It was our observation that as a group the patients with nitrogen retention did not show an average daily blood pressure lower than the group of patients without nitrogen retention (table 4). Sudden brief fluctuations appeared to be of most significance.

TABLE IV  
Average Daily Blood Pressure Readings in 64 Cases of Typhus Fever during the Febrile Period of Hospitalization \*

|                                       | Number of Cases | Average Daily Blood Pressure |
|---------------------------------------|-----------------|------------------------------|
| Cases with no nitrogen retention..... | 31              | 101/60                       |
| Cases with nitrogen retention.....    | 18              | 101/66                       |
| Fatal cases.....                      | 15              | 100/65                       |

\* Footnote as in table 1.

*The Degree of Nitrogen Retention and the Severity of the Clinical Course.* In general it was observed that the degree of azotemia as measured by the elevation of the blood non-protein nitrogen was correlated with the severity of the clinical course of typhus fever. Table 5 shows the range of the highest levels of the blood non-protein nitrogen recorded in each case with the average of the maximum values for each group of cases, classified according to the severity of disease. Although there is considerable overlapping of non-protein nitrogen values between the groups of cases, it is apparent that in general the highest blood non-protein nitrogen levels were found in the most severely ill patients.

*The Relationship between Nitrogen Retention and the Output of Urine.* It has been difficult to obtain precise data on the output of urine in many

of our patients. Incontinence is common during the course of typhus, particularly during the critical second week of the disease. Although catheterization was done on many of our patients, it was not possible to anticipate incontinence in every instance. Special nursing procedures served to reduce the volume of urine lost.

TABLE V

The Concentration of the Blood Non-Protein Nitrogen Compared with the Severity of the Clinical Course of Typhus Fever

| Classification of Severity* | Number of Patients | The Range of Maximum Values for Blood Non-Protein Nitrogen of the Patients in Each Classification | Average of the Maximum Concentration of Blood Non-Protein Nitrogen in Each Classification |
|-----------------------------|--------------------|---|---|
|                             |                    | mg. per 100 c.c.  | mg. per 100 c.c.  |
| "C"                         | 4                  | 47-74   | 58  |
| "D"                         | 9                  | 58-117  | 69  |
| "E"                         | 5                  | 72-162  | 92  |
| "F"                         | 14 †               | 75-200  | 120   |

\* Footnotes as in tables 1 and 2.

† In one of the 15 fatal cases the blood urea nitrogen only was determined; the value was 150 mg. per 100 c.c.

The development of nitrogen retention was frequently associated with a definite decrease in the output of urine, particularly in the cases which had a sudden decrease in blood pressure (charts 5, 6, 7, 8). On admission to the ward, critically ill patients with azotemia sometimes showed a low output of urine, associated with low 24 hour urine specific gravities, and low blood pressure (chart 4). In certain cases, for example case No. 5769, the decrease in fluid intake and the rise in the specific gravity of the 24 hour urine output indicated that the lowered urine volumes observed under these conditions were due probably in large measure to the decreases in fluid intake. In other cases cited above decreases in the output of urine did not appear to be as closely associated with decreased fluid intake as with a fall in blood pressure.

In patients whose 24 hour urine outputs ranged above 2000 c.c. during the febrile period, nitrogen retention was rarely observed.

An additional observation of considerable importance with relation to renal function in typhus was the presence or development of a low, or comparatively low, specific gravity of the 24 hour urine specimens in the majority of cases with azotemia and low urine volumes (charts 3, 4, 5, 7, 8, 9, 10). Consideration of these findings is reserved for the *Comment*.

*Nitrogen Retention and Its Association with Dehydration.* Abnormal concentration of the blood non-protein nitrogen is a common observation in typhus patients who demonstrate evidence of dehydration by physical examination, by observations on the output of urine, or by determination of the plasma protein and hematocrit. In such cases dehydration may be of considerable importance in the development of azotemia.

In a simultaneous study of 14 Cordon patients and 12 Commission ward

patients it was found that dehydration was present in nine of the former group and in two of the latter group. Azotemia was present in 13 of the 14 Cordon patients and in four of the 12 Commission ward patients.

Although the output of urine in the case of the Cordon patients could only be estimated, these differences in the incidence of nitrogen retention between the Cordon and Commission ward patients were believed due, for the most part, to emphasis placed on fluid intake in the care of patients in the Commission ward and the consequently large daily urine volumes in the latter group.

The concentrations of blood non-protein nitrogen in Cordon patients dying of typhus were much higher in general than on the Commission ward. Studies of the plasma proteins and hematocrit levels showed a steady increase in values up to the time of death. In one fatal Cordon case the concentration of the plasma proteins rose in 11 days from 7.0 gm. per 100 c.c. to 11.5 gm. per 100 c.c. 48 hours before death. During the same period the blood non-protein nitrogen rose from 141 mg. per 100 c.c. to 277 mg. per 100 c.c. In this case, as in many another seen in the Cordon, there was no doubt that insufficient fluid intake with a consequent reduction in the output of urine was of great importance in the degree of azotemia observed.

The clinical features of typhus predispose to dehydration to such an extent that it is difficult to combat the development of this condition with the best nursing facilities available in typhus areas. This difficulty is found particularly in the critically ill cases. It is doubtful whether dehydration played a significant part in the initiation of nitrogen retention in a number of the fatal cases observed on our ward, but as the disease progressed a reduction in urine volumes with an increase in urine specific gravity indicated that dehydration was present and probably contributed to the increase in nitrogen retention which occurred.

*Nitrogen Retention and Nephritis in Typhus.* Albuminuria was present in all patients during the febrile period of the disease, and in many instances persisted for some weeks during the period of convalescence.

Red cells and white cells were frequently noted in the sediment, often in large numbers. Frequent catheterization and the high incidence of Bilharzia in our patients, however, do not permit one to interpret the presence of red cells and white cells as evidence of nephritis. Infrequent examinations of the urine may not disclose the fact that a patient has Bilharzia. Daily examination of the concentrated urine sediment may show eggs in but a single urine specimen over a period of weeks. Cellular elements in the urine sediment of all our cases must, therefore, be interpreted with considerable caution.

Cellular casts were rarely seen. A notable exception was case No. 1109. The course of events in this patient's illness is considered in detail in the *Comment*.

The finding of numerous granular casts in the urine sediment was associated with azotemia in many cases. In some instances the number of casts

seen in the microscopic field appeared to vary indirectly with the urine volume. On occasions, however, this relationship was not clear-cut (chart 5). Rarely were granular casts absent at the time of death (charts 5, 8).

In summary it may be said that there was no conclusive evidence that typhus had produced acute glomerular damage leading to hematuria. There was, however, evidence for tubular damage in many cases which developed azotemia.

*Residual Impairment of Kidney Function Associated with Typhus Fever.* Follow-up studies on our cases with severe nitrogen retention are too few to enable us to state definitely whether or not residual impairment of kidney function is a sequel to apparent severe renal insufficiency in typhus.

Two patients admitted to the Commission ward in 1943 developed severe renal insufficiency associated with oliguria and low urine specific gravities, hypotension and azotemia. They were "E" cases. At the time of discharge from the hospital, the concentrating power of the kidneys appeared normal. Albuminuria was intermittent. Twelve months following their illness, the physical examination was negative. Observation of the urine sediment, as well as the concentration-dilution test of renal function and urea clearance showed no evidence of renal disease or impairment of kidney function.

Two additional "E" cases were observed in follow-up studies for nine months to 15 months after their disease. These patients showed albuminuria, hyaline and granular casts in the urine sediment. They were unable to concentrate the urine above 1.018 on the overnight concentration test. The urea clearance was determined in one of the cases and found to be normal. One of these cases, No. 1109, was found to have a slight elevation of his diastolic blood pressure under resting conditions. No history of previous renal disease or infections resulting in possible renal disease could be obtained from these patients. However, the possibility of renal disease existing before the onset of typhus cannot be excluded.

Numerous patients on the Commission ward who were classified as "C" or "D" patients and who showed nitrogen retention, albuminuria and cylindruria during the acute phase of the disease, showed no impairment of kidney function at the time of discharge from the hospital as evidenced by examination of the urine sediment and specific gravity. In a number of these cases the urine was examined in follow-up visits and found to be negative. Our experience to date has shown that residual renal damage was not found after recovery from severe typhus with nitrogen retention except in two cases. In these patients, renal disease may have been present prior to the onset of typhus.

*Presentation of Cases.\** The cases described below illustrate some of the phenomena associated with nitrogen retention in typhus. All of these

\*The determinations of the blood non-protein nitrogen, urea nitrogen, and creatinine were done by the methods given in War Department, Technical Manual 8-227, "Methods for Laboratory Technicians," U. S. Government Printing Office, October 1941.

The determinations of the serum proteins were done by the method described by J. S. Simmons and J. C. Gentzkow, "Laboratory Methods of the United States Army," Lea and

patients were studied on the Commission ward. The clinical records are summarized, and charts have been included to illustrate the important data.

#### CASE REPORTS

*Case No. 5508*, male, age 25, "D" severity, was admitted on the fourth day of disease with the complaints of severe headache, pain in the back and knees. The day following admission the physical examination was as follows: Temperature 40.5° C. p.r. Pulse 120. Respirations 42. Blood pressure 106 mm. Hg systolic and 68 mm. diastolic. Weight 148 pounds. The patient was well-developed and muscular. His mental state was dull. There was no deafness. An extensive maculo-papular rash was present, covering the body from the neck to the feet. A few petechial spots were seen on the inner surface of one arm. The eyelids appeared edematous. The conjunctivae were lightly suffused. The tongue was moist and white coated. A few coarse rhonchi were heard over both lower lung fields. There was no cardiac enlargement to percussion. The heart sounds were of low intensity. The rate was rapid, the rhythm regular. No murmurs were heard. The spleen was felt to descend 3 cm. below the costal margin and was not tender.

*Admission laboratory data.* Hemoglobin 89 per cent ( $\text{CuSO}_4$ ); red blood cells 4,320,000; white blood cells 1,900 with 71 per cent polymorphonuclear cells. Urine: dark amber in color, cloudy; reaction acid; specific gravity 1.018; albumin 2+. A few squamous epithelial cells, 20-25 white blood cells, a rare red blood cell and 1-2 granular casts per low power field were seen in the centrifuged sediment. The blood non-protein nitrogen was 41 mg. per 100 c.c. The urea clearance was 86 per cent of normal. The serum proteins were 6.9 gm. per 100 c.c.; albumin 4.1 gm. per 100 c.c.; globulin 2.8 gm. per 100 c.c. The roentgenogram of the chest showed small shadows scattered throughout both lung fields. The electrocardiogram was within normal limits.

*Hospital course* (chart 1). The patient ran a severe course of typhus with continuous fever for 26 days. From the fourth day to the eleventh day of disease constant sponging was employed in an attempt to reduce the fever. The rash increased, the face became dusky, the conjunctivae very injected. He developed extreme deafness, delirium, a stammering speech, and tremors of the extremities. An apical gallop

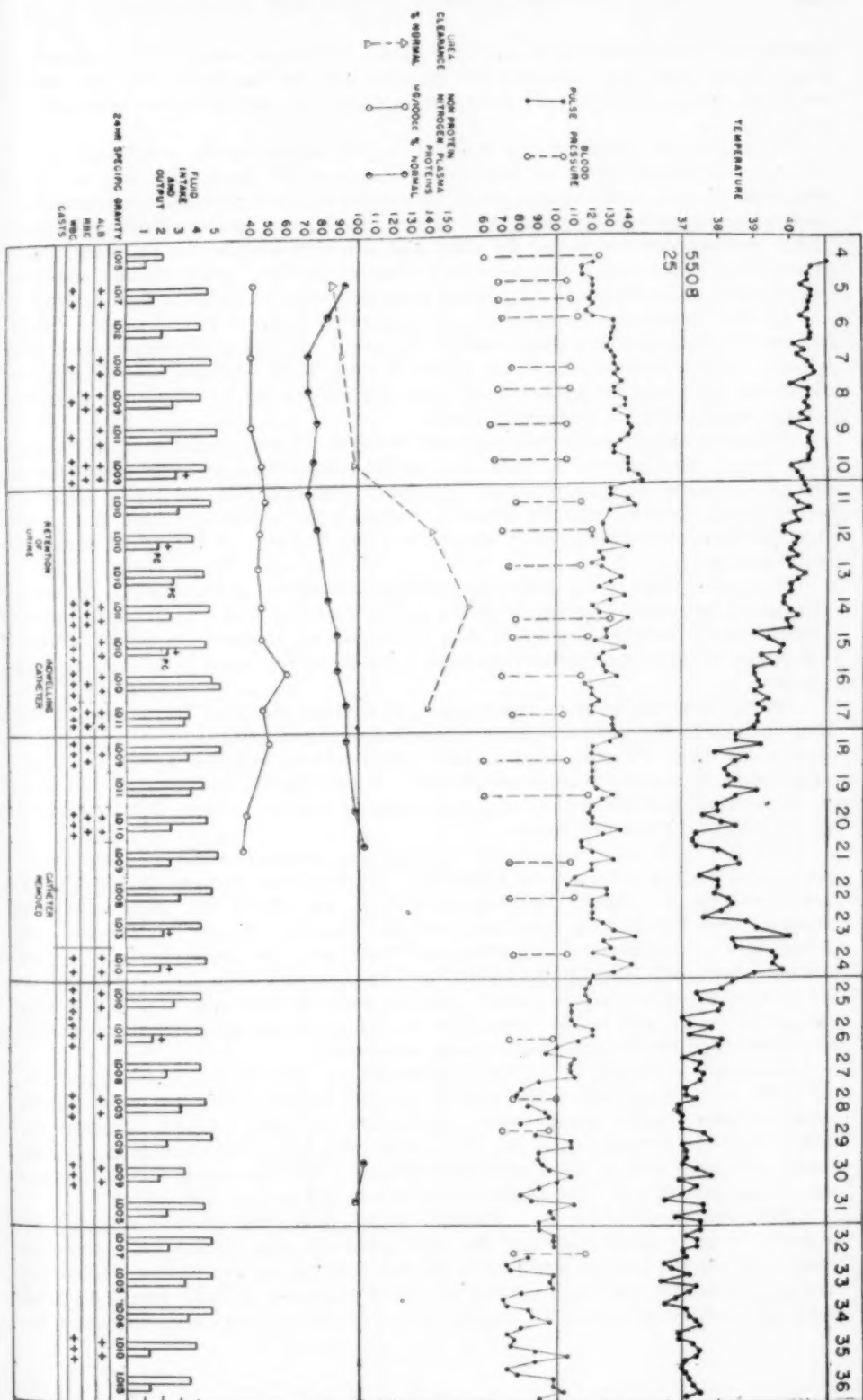
Febiger, 1944, p. 221. Roentgenograms were taken with a portable Picker U. S. Army Field Unit. Electrocardiograms were taken with a Cambridge "Simpli-trol" Portable Electrocardiograph. In many cases, the values for plasma proteins, hemoglobin, and hematocrits were determined by the method of R. A. Phillips, D. D. van Slyke, V. P. Dole, K. Emerson, Jr., P. B. Hamilton, and R. M. Archibald, "The Copper Sulphate Method for Measuring Specific Gravities of Whole Blood and Plasma," *Bumed News Letter*, Navy Department, Vol. I, No. 9, June 25, 1943.

Catheterization was done for all urea clearance tests on febrile patients. The method of Technical Manual 8-227 was used for the determination of urine urea nitrogen. The calculation of the urea clearance followed the method of E. Moller, J. F. McIntosh and D. D. van Slyke as presented by Peters and van Slyke, "Quantitative Clinical Chemistry," Vol. II, 1943—Methods, p. 564-572.

In the case reports the term " $\text{CuSO}_4$ " following the values for hemoglobin signifies that the hemoglobin concentration was measured by the copper sulphate method of Phillips et al. (see above).

The numbers at the top of the chart refer to days of disease. The temperature is recorded rectally in degrees Centigrade. A temperature of 37.5° C. or above was considered as evidence of fever. Plasma protein determinations, charted as per cent of normal, were done by the method of Phillips and his coworkers (see text). The letter "P" over the fluid intake column signifies that a part or all of the fluid intake was by parenteral route on that day. The plus mark over the fluid output column signifies that a part of the 24 hour urine output was lost. The letters "CP" indicate that catheterization was used to obtain part or all of the 24 hour output of urine.

This footnote also applies to Charts 2 through 10.



rhythm was noted on the eighth day of disease. He became incontinent of urine and feces on the tenth day. Between the eleventh and the fourteenth day the patient developed urinary retention and thereafter was put on constant bladder drainage for seven days.

Throughout the second hospital week (from the eleventh to the seventeenth day of disease) the mental status of the patient remained the same. He was at times stuporous, at other times quietly delirious, completely oblivious of his surroundings. Speech was almost unintelligible. Words were run together and stammering persisted. Jerky, trembling movements of the arms and legs were present for the greater part of this time. However, it was possible to keep up his fluid intake without resorting to parenteral administration. His blood pressure continued to be well-maintained.

On the fifteenth day his temperature began to fall. There was no cough. Slight dullness to percussion and coarse râles were heard over the right upper chest posteriorly. A roentgenogram of the chest showed small, diffuse mottled shadows throughout both lung fields, particularly over the right upper lobe. On the sixteenth day the output of urine exceeded 5 liters.

The temperature slowly fell to normal between the seventeenth and the twenty-sixth day of the disease. A brief rise on the twenty-third and the twenty-fourth day was attributed to a urinary tract infection. The rash had completely faded out by the twenty-second day of the disease. Serial electrocardiograms taken during the first five weeks of hospitalization showed at times T-waves of borderline amplitude in Leads I and II.

His mental state slowly improved and appeared normal at the time of discharge. The patient lost over 31 pounds in weight during his illness and was 20 pounds underweight when he left the hospital 55 days after onset of disease. During hospitalization ova of *Schistosoma haematobium* were found on several examinations of the urine sediment.

On follow-up examination three months after onset of typhus the patient was still 11 pounds under his normal weight, complained of slight residual tinnitus and weakness in his legs. Physical examination was essentially negative except for slight objective deafness and persistent weight loss. A mild anemia was present. His urine contained many pus cells and a very slight trace of albumin. There was no evidence of diminution in renal function.

Case No. 5808, male, age 25, "E" severity, was admitted on the sixth day of disease with the chief complaint of headache. The important findings on physical examination were as follows: Temperature 40.7° C. p.r. Pulse 108. Respirations 36. Blood pressure 126 mm. Hg systolic and 66 mm. diastolic. Weight 121 pounds. The patient was moderately well-developed and nourished. He appeared mentally clear and not acutely ill. No tinnitus or deafness was present. The skin was dark. No evidence of a typhus rash was seen. The conjunctivae were negative. The tongue was white coated and moist. The chest was clear to percussion and auscultation. Examination of the heart showed nothing remarkable.

Admission laboratory data. Hemoglobin 83 per cent ( $\text{CuSO}_4$ ); red blood cells 4,500,000; white blood cells 7,550 with 81 per cent polymorphonuclear cells. Urine: amber in color, cloudy, reaction acid; specific gravity 1.028. A few squamous epithelial cells, 1-2 granular casts per low power field, 1-3 white blood cells per high power field were seen in the centrifuged sediment. The blood non-protein nitrogen was 46 mg. per 100 c.c. The plasma proteins were 6.8 gm. per 100 c.c.

Hospital course (chart 2). Throughout the first week of hospitalization the patient's fever remained high and the rash appeared, with intense conjunctival injection, the development of petechiae in the left conjunctival sac, and active delirium. The patient became very talkative and attempted to get out of bed. Intake by mouth continued satisfactorily until the twelfth day of disease. It was necessary thereafter

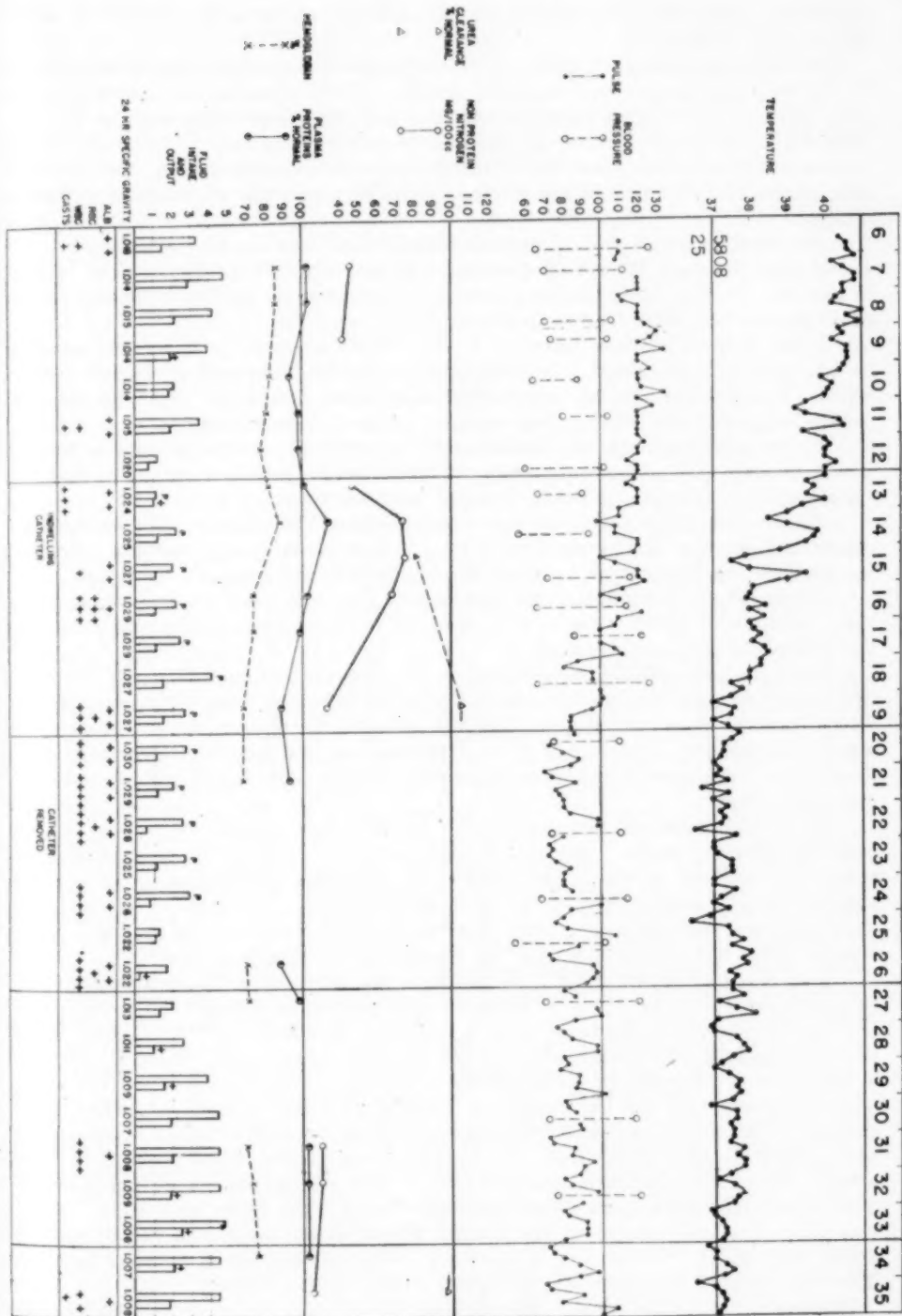


CHART 2. CASE NO. 5808.

to resort to subcutaneous injections of 5 per cent dextrose in saline and normal saline for the next 12 days.

On the thirteenth day of disease he became more stuporous and then semicomatose. He lay with half opened eyes, breathing quietly. Facial grimaces and grinding of the teeth were present. Fluid intake by mouth practically ceased. He was put on constant bladder drainage on this day because of urinary retention. His condition remained much the same from the thirteenth to the seventeenth day of disease. The rash gradually faded out during this period of time and the conjunctival suffusion disappeared.

On the seventeenth day slight improvement was noted in his mental state. He stared about the ward, his mouth open in a wide grimace. When spoken to he replied in a series of unintelligible whining sounds. There was no indication that he recognized people. The rash was no longer visible.

In the next two days he was able to obey simple commands. It was evident that he was almost totally deaf. On the twentieth day his temperature reached normal levels. Examination showed hyperactive knee jerks and ankle jerks but normal plantar response. An area of skin necrosis appeared over the coccyx.

On the twenty-second day the catheter was removed. When he was spoken to it was obvious that he was attempting to reply, but he could not articulate and the facial expressions were similar to those of a crying baby.

The area of necrosis over the lower back continued to enlarge. The patient was placed in a chair on the twenty-fourth day. A low grade fever continued. He was by that time able to eat solid food and the oral fluid intake gradually increased.

On the twenty-seventh day the patient was found to have not only hyperactive knee and ankle jerks but a bilateral positive Babinski reaction. Voluntary motion of the extremities was uncoordinated.

From this time onward improvement in his general condition was steady but slow. The ability to stand and walk unassisted returned before the ability to form words. At the time of discharge 68 days after the onset of the disease, the lesion over the coccyx was healed. Speech was slow, expressionless and labored. Hyperactive reflexes were still present in the lower extremities, but the positive Babinski phenomenon had disappeared.

On the follow-up examinations during the next four months the patient showed progressive improvement. Mentally he appeared alert. There was no residual deafness. The reflexes in the lower extremities remained hyperactive, however, and speech was still slow, labored, and monotonous in tone. Examination of the urine showed normal concentrating power, no albumin and a negative urine sediment. The anemia which had developed during the disease was no longer present.

*Case No. 1109*, male, age 35, "E" severity, was admitted on the tenth day of disease with the chief complaints of headache and buzzing in the ears. The important findings on physical examination were as follows: Temperature 39.0° C. p.r. Pulse 98. Respirations 40. Blood pressure 96 mm. Hg systolic and 66 mm. diastolic. Weight was not determined. The patient appeared well-developed, objectively deaf, and disoriented. He had no cough. A macular rash was present, extending from the neck to below the knees and involving the arms to the wrists. Some macules were fixed, others blanched on pressure. In some areas the rash appeared petechial in character. The skin of the face appeared dusky. The conjunctivae were not suffused. The tongue and oral mucous membranes were moist. The lungs were clear. There was no cardiac enlargement to percussion. Heart sounds were well heard, and the action was regular. There were no murmurs. The liver and spleen were not palpable. The extremities were negative. The deep tendon reflexes were normal.

*Admission laboratory data.* Hemoglobin 96 per cent (Sahli). Red blood cells 4,690,000; white blood cells 5,900 with 83 per cent polymorphonuclear cells. Urine:

amber in color, cloudy; reaction alkaline; specific gravity 1.010; albumin 2+; an occasional red blood cell and epithelial cell were seen in the centrifuged sediment. The blood non-protein nitrogen was 86 mg. per 100 c.c. The plasma proteins were 6.5 gm. per 100 c.c.

The electrocardiogram showed low voltage of the QRS complexes.

*Hospital course* (chart 3). The patient ran a stormy course of typhus. The rash increased during the 24 hours after admission; thereafter it began to fade, and disappeared by the twenty-seventh day of illness. He was incontinent of urine and feces during the first 10 days of hospitalization. The day following admission (the eleventh day of the disease) he was more delirious; conjunctival injection increased, and the face became quite dusky. He developed continuous twitching of the upper extremities and marked distention of the abdomen.

On the thirteenth day he was stuporous but not comatose. There was occasional twitching of the facial muscles as well as of the arms. The neck was somewhat resistant to passive flexion. An occasional rhonchus was heard over the lungs. The heart borders could not be definitely determined by percussion, and the heart sounds were obscured by phonation. An apical gallop rhythm was believed present. Abdominal distention was absent. He showed hyperactive reflexes in the lower extremities with a well-sustained bilateral ankle clonus.

During the next 48 hours his condition grew steadily more critical. Jerky movements of the facial muscles, the arms and occasionally the legs continued. The dusky hue to the face remained, but the conjunctivae showed less suffusion. The heart rate continued rapid, and a loud apical gallop rhythm was heard. The tendon reflexes in the lower extremities were still hyperactive. On the fifteenth day the electrocardiogram showed low T-waves in Leads I and II.

From the sixteenth to the nineteenth day of disease his general condition remained the same. Incontinence and deep stupor persisted. He was able to take fluids slowly by mouth. However, intravenous and subcutaneous injections of 5 per cent dextrose in saline were given to supplement the oral fluid intake.

Lumbar puncture on the twenty-first day showed a pressure of 120-130 mm. with normal dynamics. The spinal fluid was clear with 9 cells per cu. mm.

On the twenty-second day he appeared to hear when spoken to but was unable to reply except by low wails. A loose cough was present, but no sputum was obtained. Considerable lateral divergence of the right eyeball was noted for the first time. The neck was quite resistant to passive flexion. The lung fields were clear. A rough, scratching to and fro murmur was heard in the third and fourth interspace to the left of the sternum. The heart rate was still rapid; an apical gallop rhythm was present. The extremities showed considerable wasting, and there were periodic coarse tremors of both legs. The tendon reflexes in the extremities were quite hyperactive; a well-sustained ankle clonus was present. The Babinski, Gordon, and Oppenheim reactions were negative. At this time the outlook still appeared to be poor.

However, during the next four days, twenty-second to the twenty-fifth day of disease, a slow but definite improvement was noted. He became more cooperative, and could open his mouth for examination. He was even able to say a few words and ask for the bed pan, but his speech was little more than the wail of a baby. It seemed as though he were trying to learn to talk all over again. During the day he lay quietly with eyes open, his face expressionless. The precordial friction rub was still present and other physical signs remained the same.

On the twenty-seventh day of disease he complained of cramp-like abdominal pain, which was poorly localized. The white cell count on this day was 5,700 with 78 per cent polymorphonuclear cells. The urine showed many white cells, red cells, hyaline, granular and cellular casts.

On the twenty-ninth day of disease the patient appeared worse. He was pale, dyspneic, and orthopneic. In the 45° sitting position the neck veins were not distended. Examination of the heart revealed no enlargement on percussion. The heart sounds were very faint. The rate was 140-150 beats per minute. The rhythm was regular. No murmurs were heard. The lungs were clear. The abdomen was not distended, but was resistant to palpation. The liver and spleen were not felt. There was definite pitting edema over the dorsum of the feet but none over the sacral area. The systolic blood pressure had steadily decreased during the previous 72 hours and the output of urine had likewise diminished. An electrocardiogram taken the twenty-eighth day showed continuing low voltage with inverted T-waves in Lead I and flattened T-waves in Lead II. Digitalization was begun on the evening of the twenty-ninth day.

On the thirtieth day the patient was given a transfusion of 500 c.c. of citrated blood.

Gradual improvement was noted during the next three days. The dyspnea and orthopnea disappeared, and the ankle edema decreased. On the thirty-second day the electrocardiogram showed inverted T-waves in Leads I and IV and diphaseic in Lead II, with low voltage. On the thirty-third day he was put on a maintenance dose of digitalis of 0.1 gm. daily until the fifty-first day, when the drug was discontinued.

On the thirty-fifth day a purulent discharge was noted coming from the left ear, and examination revealed a perforation of the drum. He was given sulfathiazole for five days and the discharge from the middle ear ceased on the forty-first.

On the thirty-ninth day of disease he developed redness of the skin and edema of the left upper cheek and the lids of the left eye, which persisted for 48 hours.

On the forty-first day the edema of the feet was no longer present. At this time his mental condition had improved remarkably, though he still was childish in his reactions and quite deaf. He was gaining weight. The tremor and twitching had ceased, but the reflexes were still hyperactive. Examination of the heart revealed no abnormalities. The electrocardiogram showed the T-waves in Lead I to be more deeply inverted than on the thirty-second day.

On the forty-eighth day after onset of typhus he was allowed up in a chair. On the fifty-seventh day the T-waves in Leads I and II were more deeply inverted with slight depression of the S-T level, suggestive of digitalis effect.

Two months after the disease onset the urine continued to show albumin, red cells, white cells, and cellular casts. The eye grounds were first satisfactorily examined on the sixty-first day. The discs appeared normal. The arterioles were narrowed and white streaked. Arteriovenous compression and hemorrhages were not seen.

The patient was discharged from the hospital on the seventy-first day after the onset of typhus fever. It was estimated by his family that he was still 15 pounds under his normal weight. He was still quite deaf and tinnitus was present. Mentally he appeared normal. The physical examination showed nothing remarkable except for hyperactive reflexes in the lower extremities. The blood pressure was 126 mm. Hg systolic and 84 mm. diastolic. The red cell count was 3,000,000. The urine concentration-dilution test showed the inability to concentrate above 1.015 or to dilute below 1.005. The urea clearance was 117 per cent of normal, however. During convalescence ova of *Ascaris lumbricoides* and *Ankylostoma duodenale* were found repeatedly in the stools.

On follow-up examinations over a period of nine months the patient appeared in the best of health except for slight residual bilateral deafness and tinnitus. His mental state appeared to us and his family to be entirely normal. He still had residual weakness of the extrinsic muscles of the right eye. Hemoglobin values were between 90 and 100 per cent. His red cell count remained above 4,000,000. His blood pres-

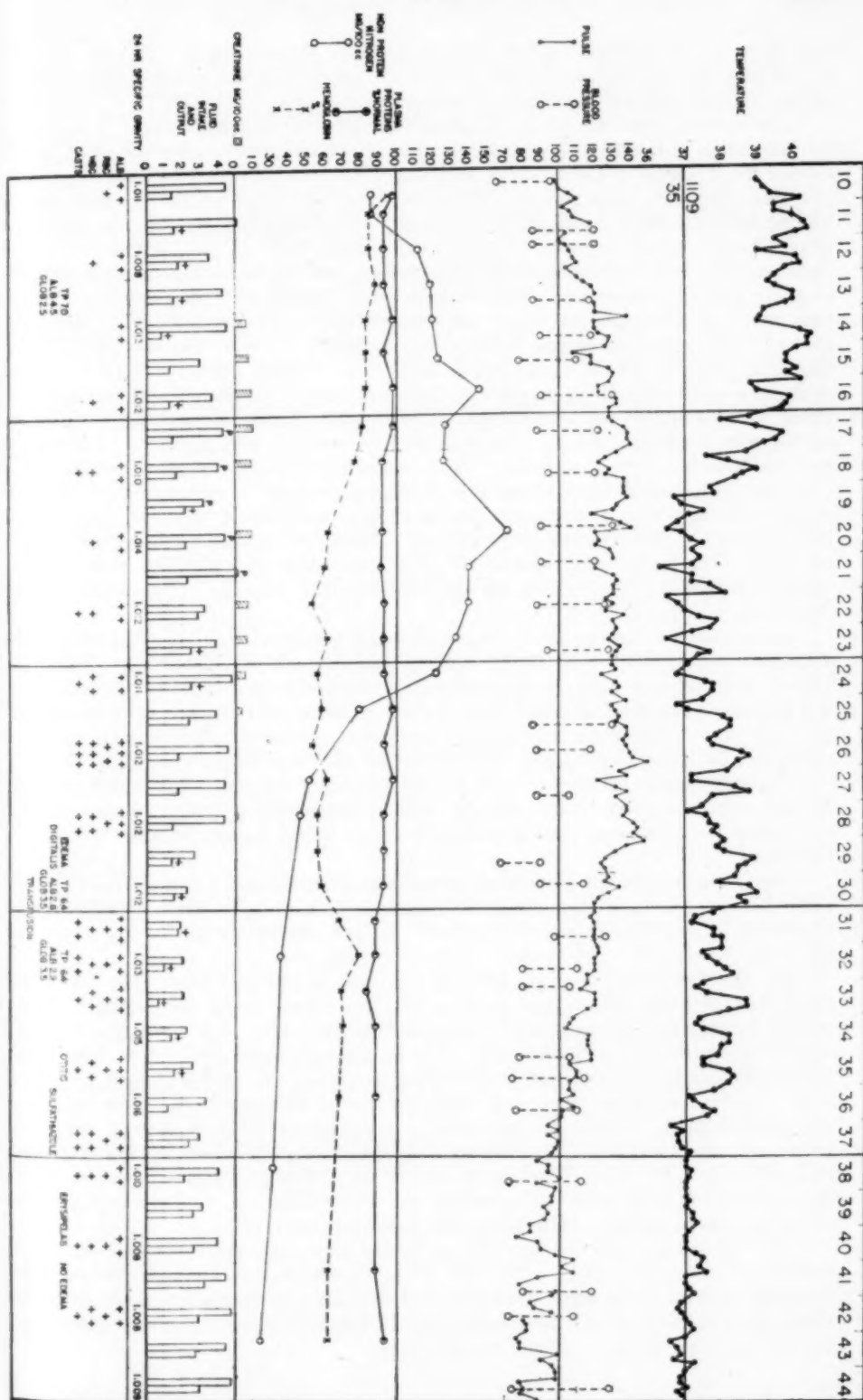


CHART 3. Case No. 1109.

sure under basal conditions varied between 128 mm. Hg systolic and 80 mm. diastolic to 140 mm. Hg systolic and 96 mm. diastolic. Repeated urine concentration tests of kidney function showed inability to concentrate the urine above 1.017.

Six months after the onset of typhus the electrocardiogram showed T-waves of low amplitude in Lead I and inverted in Lead II. Nine months after the onset of the disease the T-waves in Lead I were normal but remained inverted in Lead II.

*Case No. 4690*, male, age 45, "E" severity, was admitted on the eleventh day of disease with the chief complaint of headache. The important findings on admission physical examination were as follows: Temperature 40.0° C. p.r. Pulse 110. Respirations 38. Blood pressure 68 mm. Hg systolic and 40 mm. diastolic right arm, 74 mm. Hg systolic and 58 mm. diastolic left arm. Weight was 121 pounds. The patient was well-developed and in no respiratory distress. He was mentally clear, but drowsy. There was no objective deafness. A diffuse macular rash was present over the back, sides of the chest, and upper legs. The macules were small (2-3 mm. in diameter) and blanched on pressure. The pupils were constricted and reacted sluggishly to light and on accommodation. Three small petechial hemorrhages were seen in the right conjunctival sac. The conjunctivae were slightly injected. The tongue was moist with a light brown coat. The oral mucous membranes were moist. Several dark red petechial lesions were seen on the soft palate. There was slight dullness at the right lung base posteriorly. Coarse rhonchi were heard over both bases. The heart showed no enlargement on percussion. The first sound at the apex was of low intensity. The action was regular. No murmurs were present. The abdomen was slightly distended. The spleen tip was questionably palpable. The reflexes were depressed.

*Admission laboratory data.* Hemoglobin 83 per cent (Sahli). Red blood cells 4,130,000; white blood cells 10,950 with 85 per cent polymorphonuclear leukocytes. Urine: dark amber in color, cloudy; reaction acid; specific gravity 1.011; albumin 2+; 3-4 granular casts per low power field, 4-6 white blood cells and a rare red blood cell per high power field were seen in the centrifuged sediment. The blood non-protein nitrogen was 59 mg. per 100 c.c. The urea clearance was 50 per cent of normal.

*Hospital course* (chart 4). The patient was admitted with a low blood pressure, but the extremities were warm and the radial pulses easily palpable. Repeated catheterization was required during the first three hospital days because of urinary retention.

On the thirteenth day he became incontinent of urine and feces. Coarse rhonchi and râles were present throughout both right and left lower lobes. Disorientation continued. The blood pressure remained low, but the extremities were warm and the radial pulses full. The outlook at this time was poor.

On the fourteenth day his general condition appeared worse. He was semi-comatose. A loose cough was present, but no sputum could be obtained. Fresh petechial hemorrhages appeared in the conjunctival sacs. The tongue was moist, with a brownish coat. Coarse râles were heard throughout both lower lung fields. The heart sounds were not well heard owing to phonation. The abdomen was negative. The radial pulses were soft with occasional dropped beats. The rash was still very evident. There was no edema. An electrocardiogram showed occasional ventricular extrasystoles with abnormally low QRS and T-waves of low amplitude in Leads I and II. A roentgenogram of the chest showed increased lung markings throughout both lung fields. The patient was given 2,000 c.c. of 5 per cent dextrose in saline subcutaneously. The prognosis remained poor.

On the fifteenth day he was still extremely stuporous, but responded slightly to commands and needle pricks. He was voiding spontaneously and able to take small amounts of fluid by mouth. The rash had increased in intensity. There were no other changes in physical examination from the previous day. He was given 1,000 c.c. of 5 per cent dextrose saline subcutaneously.

On the sixteenth day he appeared definitely improved. He was able to respond slowly to questions, and was taking more fluids by mouth. He appeared to be quite deaf. He was voiding satisfactorily, though incontinent. The blood pressure had risen considerably.

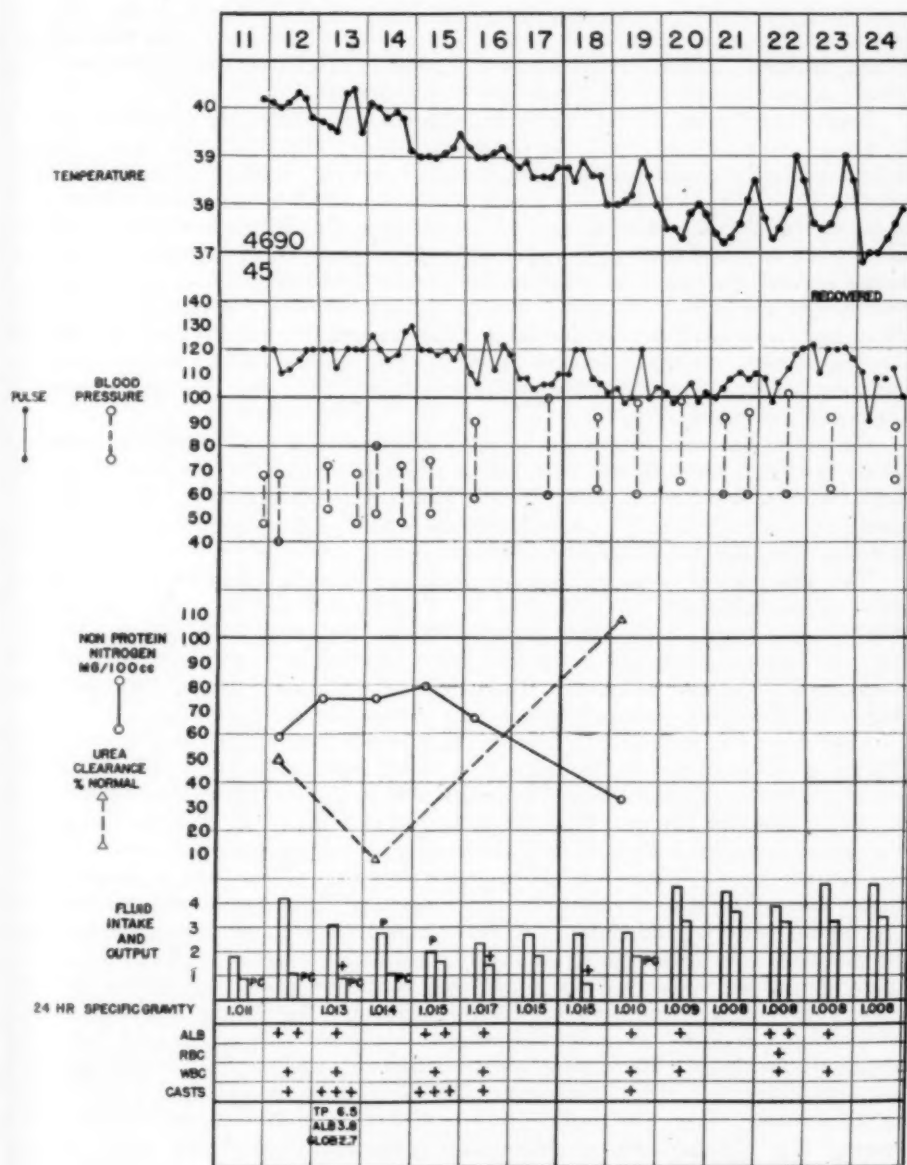


CHART 4.\* Case No. 4690.

\* In chart 4 the value for the urea clearance on the fourteenth day of disease is incorrectly charted as 8 per cent of normal. The true value obtained was 25 per cent of normal.

Improvement in his general condition continued in the next 48 hours. At times he was incontinent of stools. Mentally he appeared brighter, but for the most part lay quietly, with an apathetic expression. The cough was still present and he was raising small amounts of white sputum. The face became lighter in color, conjunctival suffusion had disappeared and the conjunctival petechiae were fading. The tongue appeared more moist. There was percussion dullness at both lung bases with fine inspiratory râles over both lower lobes. The heart and abdomen were without significant findings. The extremities appeared slightly spastic to passive motion. The reflexes appeared normal. The rash was rapidly fading.

Improvement from the eighteenth day onward was rapid. He continued to run a low grade swinging fever until the twenty-eighth day after the onset of his disease. This was associated with a cough and slowly resolving signs of pulmonary congestion over the right lower lobe, the development of a small area of skin necrosis over the tip of the coccyx, and furunculosis of the scalp. On the twentieth day of disease an electrocardiogram showed T-waves flattened in Lead I and inverted in Lead IV. On the twenty-fifth day after onset of the disease the T-waves in Lead I again became upright but of low amplitude. On the thirtieth day the T-waves in Lead I were still of low amplitude but were normal in Leads II and IV. At the time of discharge from the hospital, the thirty-seventh day after onset, he was still 14 pounds under his admission weight. The tip of the spleen was barely palpable. The urine contained no albumin, but many white cells.

On follow-up examination one month after discharge the patient had gained 12 pounds in weight but was still two pounds under his weight at the time of his first admission. He had been working steadily and had no complaints. The physical examination was negative. His blood pressure was 96 mm. Hg systolic and 68 mm. diastolic. He appeared in the best of health.

Two and one-half months after his discharge he returned again for 10 days of follow-up examinations. At this time he weighed 124 pounds. The physical examination was negative, the blood pressure 90 mm. Hg systolic and 60 mm. diastolic. His blood count was normal. Repeated urine examinations at this time showed no albumin and a negative sediment. The urine specific gravity ranged between 1.002-1.018. The blood non-protein nitrogen was 25 mg. per 100 c.c.

*Case No. 3307*, male, age 36, fatal case, was admitted on the fifth day of illness with the chief complaints of headache, pain in the legs and back. Physical examination on admission was as follows: Temperature 40.5° C. p.r. Pulse 116. Respirations 34. Blood pressure 124 mm. Hg systolic and 68 mm. diastolic. Weight 132 pounds. The patient appeared well-developed, moderately well-nourished, and acutely ill. He was mentally alert. There was no objective deafness. There was a nonproductive cough. Examination of the skin showed a macular rash, distributed over the back, upper chest, buttocks and thighs. A few isolated macules were seen on the arms. The macules were light pink in color, blanched under pressure, and developed very rapidly during the succeeding six hours after admission. The skin of the face was dusky. The conjunctivae were moderately suffused. The tongue was white coated and moist. A draining furuncle was present on the left side of the neck, below the hairline of the scalp. There were coarse inspiratory and expiratory wheezes heard over both lower lung fields posteriorly. The heart was not enlarged to percussion; the sounds were of normal quality, the rhythm was regular and no murmurs were present. The abdomen was distended and tympanitic. No organs were palpable. There was no tenderness. The remainder of the physical examination was negative.

*Admission laboratory data.* Hemoglobin 85 per cent (Sahli); red blood cells 3,420,000; white blood cells 6,950 with 77 per cent polymorphonuclear cells. Urine: amber in color, cloudy; reaction acid; specific gravity not measured; albumin 3+; many granular casts, 15-20 white blood cells and occasional red blood cells were seen in the centrifuged sediment. The blood non-protein nitrogen was 28 mg. per 100 c.c.

The total serum proteins were 7.1 gm. per 100 c.c.; albumin 4.3 gm. per 100 c.c.; globulin 2.8 gm. per 100 c.c.

*Hospital course* (chart 5). The patient had a high fever during the first three days of hospitalization, requiring frequent sponging to keep his temperature below 40.5° C. The rash continued to increase and he became progressively more stuporous.

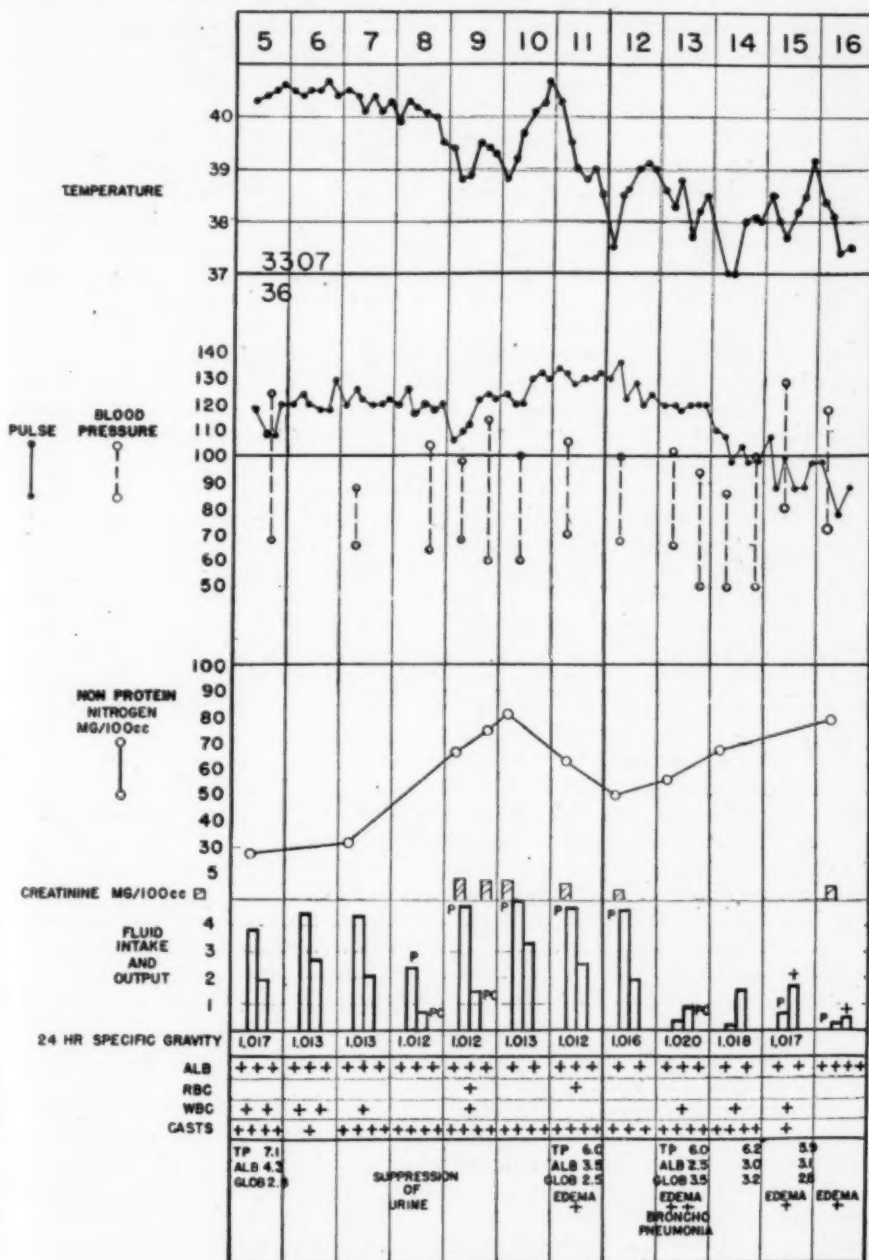


CHART 5. Case No. 3307.

On the evening of the seventh day he developed continual hiccoughs. On the eighth day his stupor had increased. It was difficult for him to take fluids by mouth. He had a cough productive of whitish sputum. He was disoriented. The face was dark blue in color. The conjunctivae showed considerable suffusion. The pupils were constricted and reacted sluggishly to light. The tip of the tongue appeared dry. The mucous membranes of the mouth were moist. The neck was not stiff. There were a few fine inspiratory râles at the left lung base. The area of cardiac dullness was not increased. The rhythm was normal. No murmurs were heard. The abdomen was slightly distended. No organs were palpable. There was no tenderness. The extremities were negative, the reflexes normal. The rash was now profuse and generally distributed over the back, chest, abdomen, arms, and legs. Numerous petechiae were present over the lower legs. The macules were of varying size; all appeared to blanch on pressure. The furuncle on the neck was draining satisfactorily. A roentgenogram of the chest showed small round shadows diffusely scattered throughout the lower left lung field. An electrocardiogram revealed QRS complexes of low amplitude. The patient did not void between 7:30 a.m. and 4:30 p.m. On catheterization 290 c.c. of dark amber, turbid urine were obtained. He was given 1,000 c.c. of 5 per cent dextrose in saline subcutaneously.

On the ninth day his stupor and delirium increased. The hiccoughs continued. There were occasional coarse tremors of the arms. The facial duskiness was more evident and the eyelids appeared puffy. The rash was more profuse. He was unable to void for the first 10 hours of the day. Four hundred and twenty-five c.c. of turbid urine were obtained by catheterization in the morning. He was given 4,000 c.c. of 5 per cent dextrose in saline by slow infusion during the day. At 4:00 p.m. he voided spontaneously and continued to do so during the night. A sputum specimen showed a moderate number of gram-positive and gram-negative cocci and diplococci. There were very few polymorphonuclear cells in the sputum smear.

On the tenth day there was slight improvement in his general condition. He was able to respond slowly to questions. His only complaint was hiccoughs. There was no essential change in the physical signs, save that many of the macules were becoming dark and fixed. The infusion of dextrose in saline was continued. The output of urine had increased and he was voiding well.

On the eleventh day he appeared sicker. The hiccoughs had lessened in frequency and severity, but his respirations had increased to 46 per minute. The cough was still present and the sputum had become purulent. The face was still very dusky. The pupils were constricted, and the conjunctivae were still suffused. The mucous membranes of the mouth were moist. Numerous hemorrhagic spots had appeared on the right buccal mucosa. There was no dullness over the lung fields to percussion, but coarse rhonchi were present throughout both lower lobes. There was no increase in the area of cardiac dullness. The heart sounds were strong. An apical gallop rhythm was present. The abdomen was not distended. The spleen was felt to descend 4 cm. on inspiration. The edge was soft and apparently not tender. The liver was not palpable. There was no twitching of the extremities. However, slight pitting edema of the feet was present. The reflexes were not abnormal. The sputum was yellowish, mucopurulent, and showed numerous polymorphonuclear cells with gram-positive diplococci and cocci in chains and a few pleomorphic gram-negative organisms. The white cell count was 12,150 with 80 per cent polymorphonuclear cells. A roentgenogram of the chest showed small discrete shadows which were diffusely distributed throughout both lungs, particularly in the lower half of each lung field.

On the twelfth day the patient appeared more alert. The hiccoughs ceased. The respirations appeared labored. There was slight dullness to percussion over the lower lung fields with coarse râles. The area of cardiac dullness was not increased. The rate was rapid and an apical gallop rhythm was still present. The abdomen was

slightly distended. There was no increase in edema over the previous day. An electrocardiogram showed increasingly low voltage of the QRS complexes with low amplitude of the T-waves in Leads I and II. A slow infusion of 3,000 c.c. of 5 per cent dextrose in saline was given. He was not able to take more than 100 c.c. of fluid per hour by mouth.

On the thirteenth day the patient's condition was much more critical. He was orthopneic. Respirations were 54 per minute, and tracheal râles were heard. There was no cough. The face was still dusky and the pupils constricted. The tongue appeared dry. There was dullness at the left lung base with coarse inspiratory râles and bronchial expiratory wheezes over both lower lung fields. The heart sounds were obscured by lung sounds, but an apical gallop was still detected. The abdomen was slightly distended and tympanitic. The pitting edema of the feet had increased. There was pitting edema of the thighs. The hands and feet were warm. There were no tremors.

The patient's condition grew rapidly worse throughout the morning. The tracheal râles became louder, the nail beds cyanotic. Postural drainage produced a considerable amount of frothy, purulent appearing material which on smear contained many polymorphonuclear cells and great numbers of gram-negative and gram-positive cocci. The patient was given oxygen by nasal catheter, 0.0015 gm. of strophanthin "G" intravenously, and 10,000 units of penicillin intravenously followed by 150,000 units intravenously during the next 12 hours. Postural drainage was continued at intervals throughout the afternoon and evening. The edema increased throughout the day. There was considerable swelling of the lower back, the hands, and arms. By evening, however, the cyanosis had lessened so remarkably that oxygen was discontinued. He was able to comprehend orders. An electrocardiogram taken five hours after the administration of strophanthin showed no changes from the tracing of the previous day. Intake by mouth during this 24 hour period was 400 c.c.

On the morning of the fourteenth day the patient appeared slightly improved. Tracheal râles were still present but less audible than on the previous day. The respiratory rate and heart rate were decreasing. The patient was still quite stuporous, however. Examination of the lungs showed dullness over the left lower lobe posteriorly and in the left axilla. There was no increase in the area of precordial dullness. The heart sounds were strong, the rhythm regular, and no murmurs were heard. The abdomen was slightly distended without evidence of free fluid. The rash was becoming less evident. There was no decrease in the peripheral edema. He was given 0.001 gm. of strophanthin "G" intravenously. The patient continued to void throughout the day and was tried on small amounts of fluid at intervals. However, he appeared to experience considerable pain in swallowing. Examination of the mouth revealed large amounts of thin, gray, purulent material in the oropharynx. No focus was seen in the parts of the mouth or throat which could be examined. On smear this material showed numerous polymorphonuclear cells, a rare gram-positive coccus and diplococcus and a few gram-negative diplococci. Examination was difficult owing to the patient's resistance, but it appeared that the pus was originating from some focus lower in the pharynx, possibly the esophagus.

On the fifteenth day he was still extremely stuporous, coughing occasionally but apparently raising very little sputum. The respirations were deep and regular and 40 per minute. The examination of the chest revealed no changes. The blood pressure had risen considerably in the preceding 24 hours. A large, dark bluish area was present in the skin over the lower sacrum. The patient was given 100 c.c. of concentrated human albumin intravenously followed by 50 c.c. of normal saline. The edema appeared to decrease throughout the day.

On the morning of the sixteenth day the patient was more stuporous and could hardly be roused. The respiratory rate was 40 per minute, the breathing quiet and

regular. An occasional loose cough was not productive of sputum. There was dullness over the left lower lung field to the lower border of the scapula with moist sounding râles, but no evidence of consolidation. A few râles were heard over the right lower lobe. The heart showed no evidence of dilatation, the sounds were strong, the rhythm regular. The abdomen was soft. The edema had decreased markedly since the previous day. The large bluish area of skin over the sacrum was still intact. He was given 250 c.c. of plasma intravenously in the morning. He gradually became more comatose throughout the day. Respirations ceased suddenly at 4:00 p.m.

A postmortem examination was performed one and one-half hours after death by Lieutenant Commander W. B. McAllister, Jr.; the important gross findings were as follows:

The body was that of a well-developed, well-nourished, light-skinned Egyptian male which weighed about 135 pounds. Rigor mortis was not present, and there was no jaundice. There was marked subcutaneous edema, all of the tissues were edematous, and there was some free fluid in all of the serous cavities. There was a diffuse macular and petechial cutaneous rash characteristic of typhus. Aside from a few pale areas in the myocardium near the epicardium, the heart was normal. The lungs, particularly the posterior portions, were congested, and in the lower lobes there were numerous small, reddish areas of early consolidation. There was a marked acute bronchitis and tracheitis. There were numerous petechiae in the buccal mucous membranes. A communication led through the socket of the left third molar, which was absent, into the left maxillary sinus. A large amount of tenacious purulent material drained from this tooth socket. Associated with this tract was another leading through the soft tissues of the lateral wall of the pharynx into a pocket which lay behind the posterior wall of the pharynx. All of the soft tissues surrounding this tract were acutely inflamed and edematous and showed numerous hemorrhagic points. The gastrointestinal tract and associated organs were essentially negative. The spleen was enlarged and the pulp was soft and friable. The kidneys were swollen and showed numerous absolutely round hemorrhagic spots on the outer cortical surfaces. A few of these were also seen in the cortical zone on cut section. There were numerous submucosal hemorrhages in the kidney pelves. The whole posterior muscular wall of the bladder and the soft tissues surrounding the rectum and overlying the sacrum were edematous and hemorrhagic. They appeared to be almost necrotic. This process extended to some extent behind the sacrum. The outer zones of the adrenal cortices were grayish in color and apparently contained less fat than normal. The central nervous system was edematous, but otherwise not abnormal grossly.

*Case No. 5769*, male, age 46, fatal case, was admitted on the probable fifth day of the disease with the chief complaints of headache and pain in the legs. On admission the important findings on physical examination were as follows: Temperature 40.3° C. p.r. Pulse 80. Respirations 32. Blood pressure 108 mm. Hg systolic and 80 mm. diastolic. Weight 114 pounds. The patient appeared older than his stated age, undernourished and mentally dull. A maculo-papular rash was present over the upper arms, back, and upper legs. The lesions blanched on pressure. The skin of the face was dusky. The pupils were small, the conjunctivae were not suffused. The tongue was moist. Harsh breath sounds and liquid sounding rhonchi were present over the left lower lobe. There was no cardiac enlargement to percussion. A questionable apical systolic murmur was present. The brachial arteries appeared thickened and tortuous, with visible pulsations.

*Admission laboratory data.* Hemoglobin 87 per cent ( $\text{CuSO}_4$ ); red blood cells not determined. Urine: dark amber in color, cloudy; reaction acid; specific gravity 1.026; albumin 2+; many squamous epithelial cells, 6-8 white blood cells and an occasional granular cast were seen in the centrifuged sediment. The non-protein nitrogen was 40 mg. per 100 c.c. The urea clearance was 122 per cent of normal. The electrocardiogram was within normal limits.

*Hospital course* (chart 6). The patient became steadily more ill throughout the first hospital week. The rash increased until the eleventh day of the disease. With the increase in rash he became progressively more drowsy. On the eighth day several light red spots were noted on the palms. The cough continued but no sputum was obtained. He was incontinent of urine. On the ninth day he vomited once and refused fluids. He was semistuporous and apparently quite deaf. On the tenth day he was stuporous but could be roused. He refused all fluids by mouth. The con-

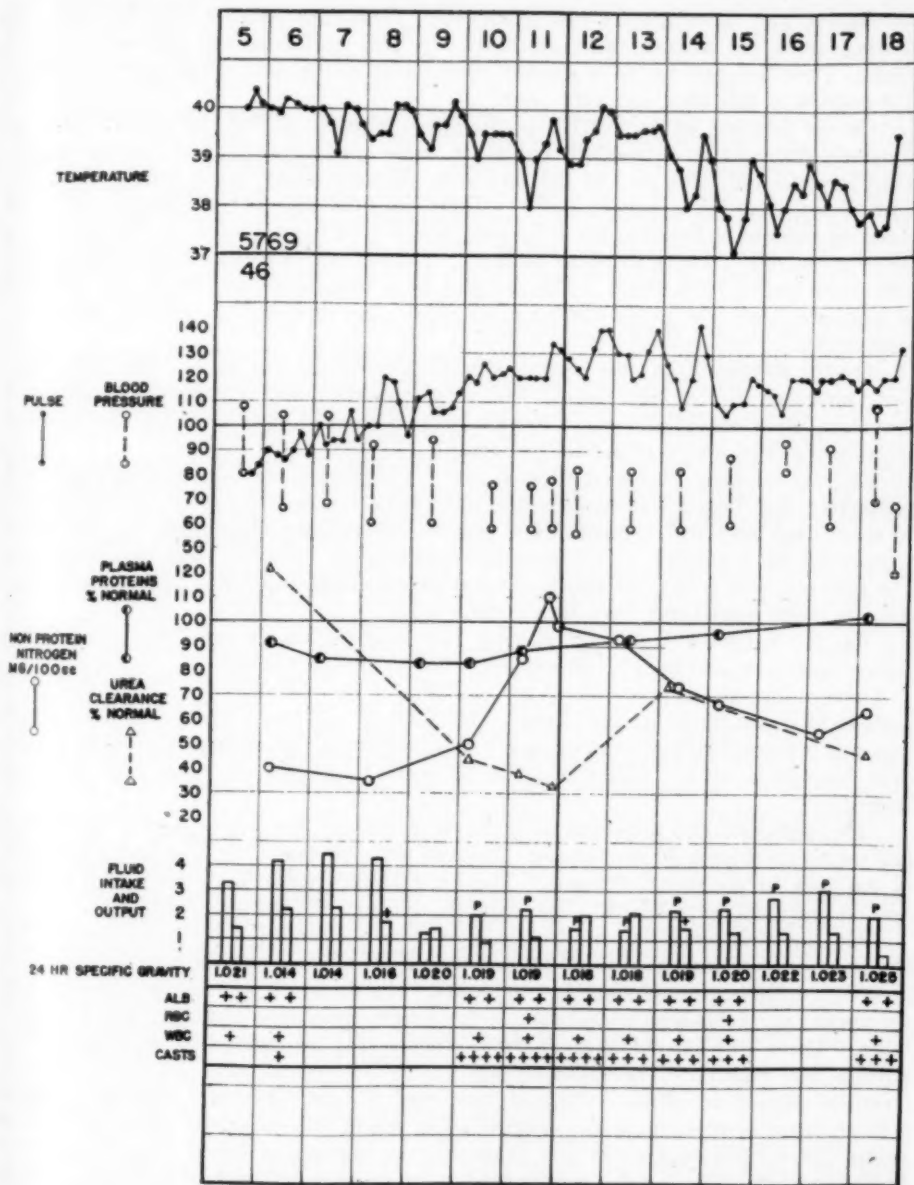


CHART 6. Case No. 5769.

junctivae were suffused. The tongue appeared to be slightly dry. The skin of the face was quite dusky. There were no changes in the chest signs from the findings on admission. The abdomen and extremities were negative. He was given 2000 c.c. of 5 per cent dextrose in saline subcutaneously. On the eleventh day the stupor had increased. The respirations were between 40 and 52 per minute throughout the day. The oral mucous membranes did not appear dry. The neck was slightly resistant to flexion. There were loud rhonchi and harsh breath sounds at the lung bases. The heart rate was rapid, the rhythm regular, and radial pulses were full. The abdomen, extremities, and reflexes were not remarkable. The rash became very profuse, and in some areas the macules were confluent. A dull erythema was present over the trunk. Two thousand c.c. of 5 per cent dextrose in saline were given subcutaneously. The outlook at this time was very poor.

On the morning of the twelfth day he appeared to be slightly improved. He was extremely drowsy and refused all fluids. A loose cough was present, but no sputum could be obtained. The skin of the face was still very dusky. The tongue showed a light brown coat but appeared moist. There was dullness to percussion and moist sounding râles were heard at the right lung base. The heart showed no changes from the previous day. There were no tremors. The reflexes were not hyperactive. The rash continued to be brilliant. The macules were both large and small and blanched on pressure. He was given 1,000 c.c. of 5 per cent dextrose in normal saline subcutaneously.

On the thirteenth day his general condition remained the same. The rash, however, appeared to be less florid. He was stuporous and completely disoriented. Parenteral fluid administration (2,000 c.c.) was continued daily until the day of death because of reluctance to take fluid by mouth.

On the morning of the fourteenth day he became quite talkative although still completely disoriented. However, restraints were not necessary. A loose, nonproductive cough was still present. The tongue and mucous membranes of the mouth appeared to be quite dry. The signs of congestion at the right lung base were less. The rash was still florid. It was noted that subcutaneous injections of 5 per cent dextrose in saline were being very slowly absorbed.

On the fifteenth day slight general improvement was noted. He was able to answer questions and breathe on request. The rash was fading.

General improvement appeared to continue on the sixteenth day. He had short periods of comparative mental clarity. His stupor was less evident. A loose cough was still present with no expectoration. Rhonchi and a few coarse râles were present over both lung fields. There was no dullness on percussion. The rash was still fading.

He appeared more stuporous on the seventeenth day, however, and the respirations had increased to over 50 per minute. He was not orthopneic. There was no increase in the area of precordial dullness. The heart sounds were loud, the action regular, and no murmurs were heard. The abdomen and extremities were negative.

On the eighteenth day of disease, however, his condition became critical. The respirations were increased to 50-60 per minute, there were audible tracheal râles, and no cough. He became profoundly stuporous. Harsh breath sounds were present over the upper lung fields with coarse râles over the left upper lobe and right and left lower lobes. There was no evidence of fluid. There was no change in heart size. The rhythm was regular. The abdomen was soft. No organs were palpable. The extremities showed no edema. The rash continued to fade. Postural drainage produced a large quantity of thin, yellow sputum. On smear this contained large numbers of polymorphonuclear leukocytes and gram-positive organisms, lancet shaped diplococci predominating. The patient was started on a regimen of penicillin therapy, but he rapidly became comatose and died.

No postmortem examination was obtained.

*Case No. 5133*, male, age 30, fatal case, was admitted on the fifth day of disease with the chief complaint of severe headache. On admission the important findings on physical examination were as follows: Temperature 40.3° C. p.r. Pulse 96. Respirations 30. Blood pressure 114 mm. Hg systolic and 70 mm. diastolic. Weight 120 pounds. The patient appeared acutely ill. A cough was present, productive of a small amount of white sputum. A diffuse maculo-papular rash was seen over the back, chest, arms, abdomen, and legs to the ankles. Several bright red macules were present on the right palm. All the lesions blanched on pressure. The conjunctivae appeared moderately suffused. The tongue was white coated and dry. Coarse rhonchi were heard over both lung fields. The heart size appeared normal to percussion. The rhythm was regular. No murmurs were heard. The spleen was felt to descend 3 cm. below the costal margin. The edge was firm, sharp, and not tender.

*Admission laboratory data.* Hemoglobin 102 per cent (Sahli); red blood cells 5,140,000; white blood cells 7,500 with 86 per cent polymorphonuclear cells. Urine: amber in color, cloudy; reaction acid; specific gravity 1.022; albumin 2+; many squamous epithelial cells and 1-3 granular casts per low power field were seen in the centrifuged sediment. The blood non-protein nitrogen was 34 mg. per 100 c.c. The plasma proteins were 7.2 gm. per 100 c.c. A roentgenogram of the chest showed prominent lung markings and areas of calcification in the right hilar region. The electrocardiogram showed T-waves of borderline amplitude in Lead I.

*Hospital course* (chart 7). The patient became progressively sicker during the sixth and seventh days of his disease and developed severe diarrhea for a period of about 16 hours. In spite of a good fluid intake his tongue remained dry; petechiae appeared on the buccal mucous membranes, and the rash became more profuse. On the evening of the seventh day against orders, he was given 3 grains of nembutal. He remained very stuporous throughout the eighth day. The abdomen became distended and hiccoughs developed. The electrocardiogram showed low voltage of the QRS complexes. He was given 1,900 c.c. of 5 per cent dextrose in saline subcutaneously, but developed suppression of urine.

On the ninth day he was more alert. The cough was less in evidence but his respirations had increased to 44 per minute, though they were not labored. He felt more comfortable in a 45° sitting position. The face was exceedingly dusky, and the conjunctivae were injected. The tongue appeared slightly dry. Coarse rhonchi, but no dullness or râles, were heard throughout the lower lung fields. The heart rate had increased. The abdomen remained distended; no organs were felt. There was no peripheral edema. The rash remained profuse. By 7:00 p.m. he had not voided for nearly 36 hours; 440 c.c. of turbid urine was obtained by catheterization. A roentgenogram of the chest revealed small round shadows throughout both lung fields.

On the tenth day the patient's condition appeared worse. Mentally he was alert. Respirations remained elevated, but not labored. An occasional cough produced small amounts of tenacious white sputum. Periodic hiccoughs were still present. The face was darkly flushed. Intense conjunctival injection persisted. The rash remained profuse. There was no distention of the neck veins in the horizontal position. The hands and feet were warm. There was slight dullness over both lung bases, with inspiratory râles and expiratory rhonchi over both lower lobes. The area of cardiac dullness was not increased. The heart sounds were obscured by breath sounds. There were occasional involuntary twitches of the hands and fingers. Fluid intake by mouth had practically ceased. The electrocardiogram showed only T-waves of low amplitude in Leads I and II. He was put on continuous bladder drainage, and given a slow infusion of 2,000 c.c. of 5 per cent dextrose in saline.

On the eleventh day he became mentally confused. The respirations remained rapid. The chest signs appeared to be the same as on the previous day. The heart rate had increased. There were no signs of peripheral venous congestion. The abdomen was no longer distended. The sputum was purulent, containing many gram-



positive organisms. Intake by mouth was still much reduced. He was given penicillin, 40,000 units intramuscularly every three hours, 400 c.c. of dextrose in saline intravenously, and 600 c.c. intramuscularly.

On the twelfth day his condition became much worse. He grew stuporous. Audible tracheal râles appeared. His lips and nail beds became cyanotic, his hands and feet grew cold. The rash had become more profuse. The blood pressure fell to 80 mm. Hg systolic and 50 mm. diastolic. Crepitant râles appeared over both lower lobes posteriorly with a small area of bronchial breathing at the right base. The heart sounds could not be heard nor the heart borders percussed. The electrocardiogram showed T-waves of low amplitude in Lead I and of borderline amplitude in Lead II, and borderline low voltage of the QRS complexes. He was given oxygen by face mask, intravenous caffeine with sodium benzoate, and 0.001 gm. of strophanthin "G." The cyanosis was reduced somewhat by the administration of oxygen and the respiratory rate became less. However, the blood pressure continued to remain low and at times the radial pulses were not felt. When the face mask was removed for a few moments the cyanosis rapidly increased and the respirations became slow and gasping. Towards evening the temperature mounted rapidly; respirations grew slower and ceased.

At postmortem examination the rash was still present. The pleural cavities contained no fluid. The lungs were well aerated, except for an area of firm tissue the size of a walnut in the right lower lobe, and small areas in the dependent portions of both lower lobes, which on section appeared red and from which reddish fluid and pus could be expressed. The heart weighed 320 gm. and was contracted. The pericardial and endocardial surfaces appeared normal. The ventricular walls were of normal thickness. The valves appeared normal. The liver weighed 1,800 gm. On section, the individual lobules were distinct. The spleen (not weighed) appeared slightly enlarged. The capsule was wrinkled, and on section the pulp appeared firm. The kidneys appeared normal in size. There were small hemorrhages in both renal pelvises. There were several small areas of submucosal hemorrhage in the wall of the bladder. The brain weighed 1,200 gm. The convolutions of both hemispheres appeared shrunken. There was no evidence of edema. The remainder of the post-mortem examination was grossly not remarkable.

*Case No. 7250*, male, age 30, fatal case, was admitted in the fourth day of the disease with the chief complaint of headache. On admission physical examination the important findings were as follows: Temperature 40.0° C. p.r. Pulse 88. Respirations 36. Blood pressure 118 mm. Hg systolic and 64 mm. diastolic. Weight 116 pounds. The patient appeared moderately ill, mentally clear, with rapid respirations, and no cough. A few poorly defined maculo-papular lesions were noted over the chest, abdomen and arms. The conjunctivae appeared moderately injected. The tongue was moist. A few crepitant râles were heard on the right mid lung field posteriorly. Examination of the heart was not remarkable. The spleen was enlarged, but not tender. Its tip was felt 7 cm. below the costal margin. The liver was not palpable, but enlarged 3 cm. below the costal margin by percussion.

*Admission laboratory data.* Hemoglobin 72 per cent ( $\text{CuSO}_4$ ); red blood cells 4,110,000; white blood cells 4,300 with 76 per cent polymorphonuclear cells. Urine: amber in color; reaction acid; specific gravity 1.023; albumin 2+; 8-10 white cells per high power field, and an occasional granular cast were seen in the centrifuged sediment. The blood non-protein nitrogen was 30 mg. per 100 c.c. The plasma proteins were 6.5 gm. per 100 c.c.

*Hospital course* (chart 8). In spite of frequent sponging the patient continued to run a high fever from the fourth to the ninth day of disease. On the fifth day the maculo-papular rash increased but the macules were still scanty and poorly defined. On the sixth day the patient became disoriented. On the eighth day he was quite drowsy and vomited twice. His general condition, however, appeared satisfactory.

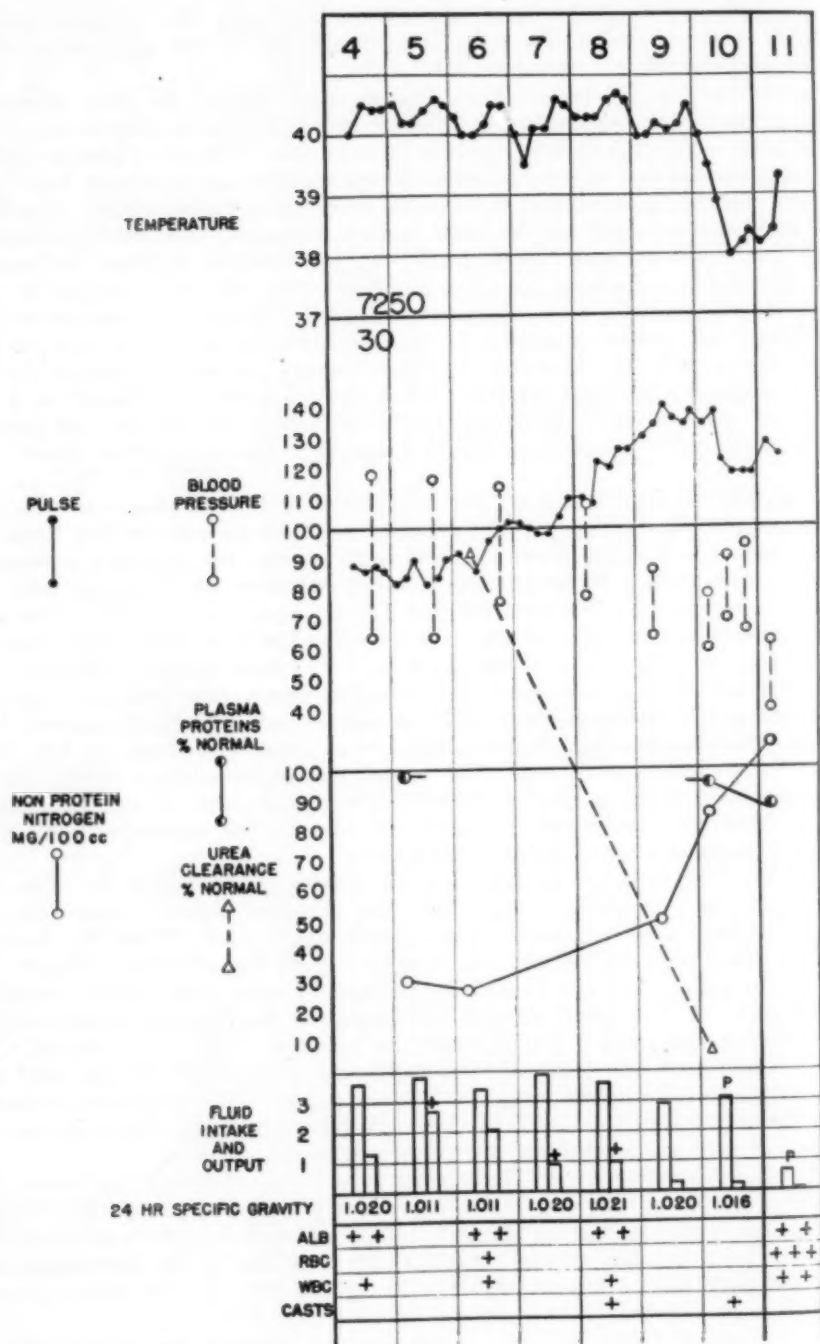


CHART 8. Case No. 7250.

On the ninth day he became semicomatose. The pulse rate had increased to between 130-140 beats per minute. The blood pressure fell. The respirations were rapid. The neck was quite resistant to passive flexion. Examination of the heart and lungs was negative. Spinal puncture revealed an initial pressure of 90 mm., and the dynamics were normal. Seven c.c. of spinal fluid were withdrawn. The final pressure was 60 mm. The cell count of the spinal fluid was 5 per cu. mm. The Pandy test was negative. An electrocardiogram showed low voltage of the QRS complexes. The patient was given 1,000 c.c. of 5 per cent dextrose in saline subcutaneously.

On the morning of the tenth day his general condition had become critical. Oliguria was present, the blood pressure was low, the heart rate still rapid. He was given 100 c.c. of concentrated human albumin intravenously. Subcutaneous injections of 0.5 gm. of caffeine with sodium benzoate were given every two hours. Slight improvement in his general condition was noted throughout the day with a decrease in heart rate and a rise in blood pressure. The state of oliguria continued, however. There was no increase in the rash from the fifth day.

On the morning of the eleventh day the patient had a generalized convulsive seizure and died.

At postmortem examination one hour after death, the interesting findings were as follows. The rash which had been scanty throughout his illness was not discernible. No gross areas of pneumonitis were noted in the right lung. The left lung was crepitant throughout. The bronchi appeared normal. The heart weighed 330 gm. There were no gross abnormalities seen on the epicardial or endocardial surfaces. The ventricular walls were of normal thickness. The coronary arteries were patent. The liver weighed 2,430 gm. It was grayish in color, firm and rubbery in consistency. The surface was lobulated, with numerous white fibrotic areas in the depressions between the lobules. On section the cut surface was gray. Areas of dense fibrosis were present throughout the organ. Numerous adult *Schistosomes* were obtained from the blood in the portal vein. The spleen weighed 770 gm. The surface was mottled with numerous white, bluish, and reddish areas, some of which were firm in consistency. On section the pulp was firm and deep red in color. The surface patches extended a few mm. into the spleen substance and appeared to be demarcated by a narrow zone of hemorrhage.

The right kidney weighed 210 gm. There were a few pin-point hemorrhagic spots on its surface. On section the cortex appeared to be slightly pale. The kidney pelvis appeared negative. The left kidney weighed 190 gm. The findings were similar to those seen in the right kidney. The ureters appeared normal and patent. The mucosa of the bladder was of light yellowish tint and was thickened. Small areas of hemorrhage were present in the region of the trigone.

The mucosa of the large intestine and rectum showed mottled areas of bluish and brownish discoloration. There were numerous elevated nodules of 0.5 to 0.7 cm. in diameter with smooth surfaces. These were not pedunculated and were pale green to blue black in color. The findings in the liver, bladder, and large bowel were secondary to an extensive *Schistosoma* infection.

*Case No. 6146*, male, age 26, fatal case, was admitted on the sixth day of disease with the chief complaints of mild headache, cough, and general aches and pains. Physical examination the morning following admission was as follows: Temperature 40.4° C. p.r. Pulse 122. Respirations 30. Blood pressure 96 mm. Hg systolic and 68 mm. diastolic. Weight 132 pounds. The patient appeared moderately ill, mentally clear, and had a hacking cough. A faint, sparse macular rash was present over the chest and back. The pupils were small, the conjunctivae moderately injected. The tongue was red with a patchy white coat. The mucous membranes of the throat appeared injected. Coarse rhonchi were present over the lower half of each lung field. The heart was of normal size to percussion. The heart sounds were distant, the

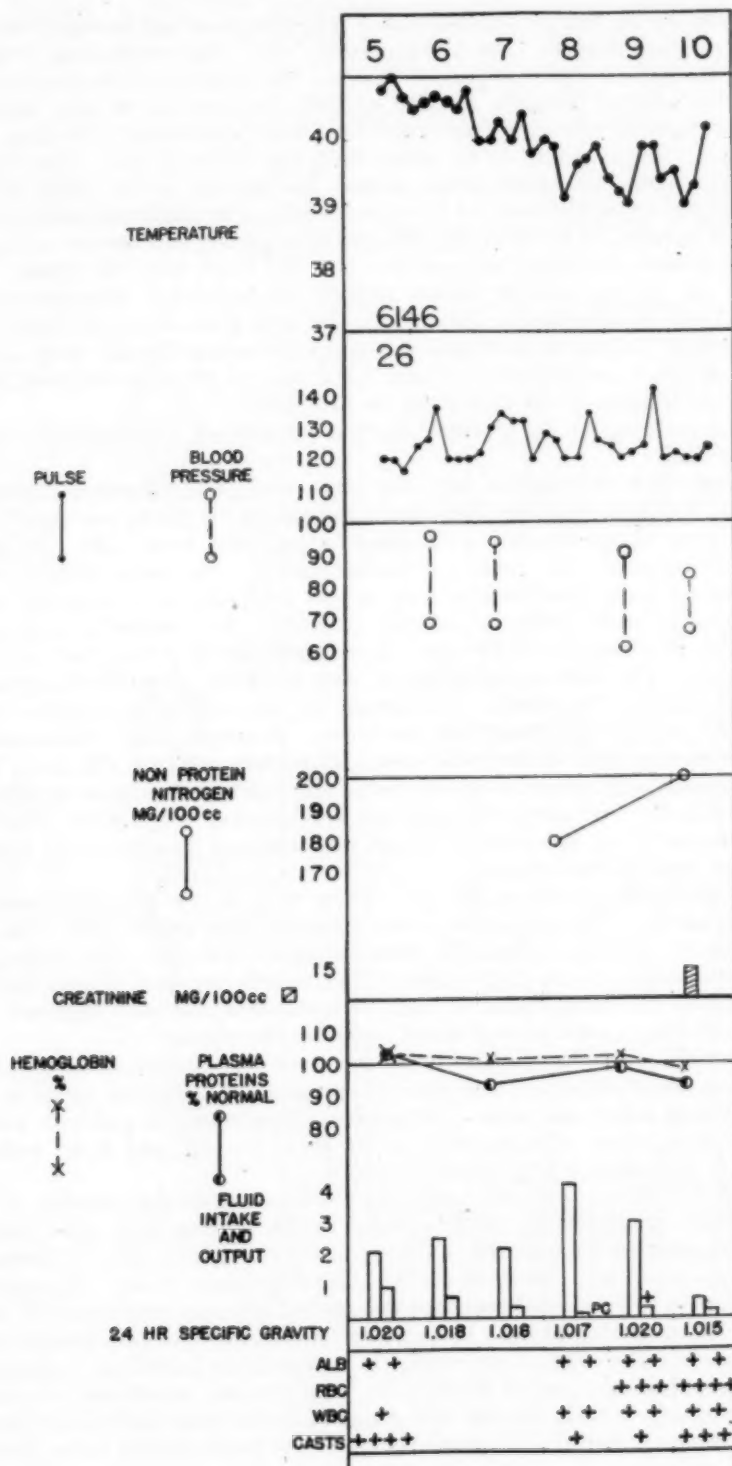


CHART 9. Case No. 6146.

rhythm was regular, and no murmurs were present. A hard, non-tender spleen was felt 3 cm. below the left costal margin.

*Admission laboratory data.* Hemoglobin 103 per cent ( $\text{CuSO}_4$ ); red blood cells 5,450,000; white blood cells 8,450 with 88 per cent polymorphonuclear cells. Urine: light amber in color, cloudy; specific gravity 1.018; albumin 2+; a few squamous epithelial cells, many granular casts; 4-6 white blood cells per low power field were seen in the centrifuged sediment. The plasma proteins were 6.8 gm. per 100 c.c. A roentgenogram of the chest showed prominent hilar shadows and small dense shadows at the left lung base which suggested areas of calcification.

*Hospital course* (chart 9). The patient vomited several times on the seventh day, and the nonproductive, hacking cough continued until the ninth day. A few more light red macules made their appearance on the trunk. There were no changes in the chest signs from the time of admission examination. On the eighth day he was unable to void. He was given 2,000 c.c. of normal saline subcutaneously, and catheterized. His condition appeared worse on the ninth day. He was slightly disoriented, had coarse tremors of the upper extremities, and picked at his bedclothes. The rash became widespread and profuse, the conjunctivae intensely injected. The tongue and mucous membranes of the mouth and throat appeared to be very dry. Examination of the lung fields showed fine crepitations over both bases. The heart sounds were not well heard.

On the morning of the tenth day he became semicomatose. The cough ceased. He developed Cheyne-Stokes respirations. The conjunctival injection increased and the rash became more profuse. A brown, dry coat appeared on the tongue. Numerous petechial hemorrhages were seen on the buccal mucous membranes. The neck was not stiff. Signs in the chest were similar to those observed on the previous day. There was marked twitching of the hands, arms, and occasionally the legs. At noon the hands and feet became cold, the lips and nail beds cyanotic. Shortly thereafter he developed a Jacksonian convulsion and died.

At postmortem examination one hour after death the following findings were of interest. An extensive rash covered the entire body except for the face and neck, palms of the hands, lower legs and feet. The pleural cavities contained no free fluid. There was a small area of firm tissue at the base of the left lung which appeared red and dry on cut section. The bronchi contained a moderate amount of viscid yellowish exudate. The mucosa of the large bronchi was intensely reddened. The heart appeared of normal size with no gross abnormalities. The spleen was of normal size, and on cut section the pulp was firm. The kidneys appeared to be of normal size, and the surfaces were smooth. Minute dark red circular spots were found on the surface of both kidneys, but on cut section there were no gross abnormalities to be seen. Small areas of hemorrhage were seen in both renal pelves and on the mucosal surface of the bladder. The left adrenal gland appeared normal. The right was not examined. The brain appeared grossly normal. The remainder of the gross examination was not remarkable.

*Case No. 7464*, male, age 43, fatal case, was admitted on the sixth day of disease with the chief complaints of headache and generalized aches and pains. On physical examination the important findings were as follows: Temperature  $39.8^\circ \text{C}$ . p.r. Pulse 100. Respirations 40. Blood pressure 100 mm. Hg systolic and 60 mm. diastolic. Weight 129 pounds. The patient's general condition appeared good; he was mentally clear and objectively deaf. There was a light erythema over the back and a few suspicious appearing spots on the anterior thighs and about the hips which suggested an early typhus rash. The conjunctivae were suffused. The tongue was moist. Coarse rhonchi were heard over the lung fields. The heart size appeared normal to percussion. The action was regular, and there were no murmurs. The spleen was enlarged 3 cm. below the left costal margin. The edge was sharp and not tender.

*Admission laboratory data.* Hemoglobin 85 per cent ( $\text{CuSO}_4$ ); red blood cells 4,020,000; white blood cells 2,550 with 81 per cent polymorphonuclear cells. Urine: amber in color, cloudy; reaction acid; specific gravity 1.010; albumin 1+; many squamous epithelial cells; 1-3 white blood cells and an occasional red blood cell per high power field were seen in the centrifuged sediment. The blood non-protein nitrogen was 25 mg. per 100 c.c. The urea clearance was 118 per cent of normal. The plasma proteins were 5.1 gm. per 100 c.c. A roentgenogram of the chest showed a generalized increase in the lung markings but otherwise appeared negative.

*Hospital course* (chart 10). During the sixth, seventh, and eighth days of disease the patient had a high fever requiring almost constant sponging to keep the temperature below  $40.5^\circ \text{C}$ . The rash became increasingly evident and the patient more drowsy.

On the ninth day slight delirium was present. The tongue and oral mucous membranes appeared slightly dry, and fine inspiratory râles were heard over both lower lung fields, but no signs of consolidation could be elicited. The sputum was yellow, blood streaked, tenacious, and contained many gram-positive organisms.

On the tenth and eleventh days the patient became progressively more stuporous; chest signs continued, but no evidences of consolidation were present. The white blood cell count on the tenth day was 11,050 with 78 per cent polymorphonuclear cells. Muscular twitching of the face was noted. On the eleventh day the rash was definite and widespread over the trunk.

On the morning of the twelfth day he was semicomatose and cyanotic. Signs of consolidation appeared over the right lower lung field. A roentgenogram of the chest showed a high right diaphragm with numerous soft shadows in the right lower lung field. An electrocardiogram showed low voltage with frequent ventricular extrasystoles. The patient was given 300 c.c. of plasma intravenously and 300 c.c. of 5 per cent dextrose in saline, and oxygen by face mask. Penicillin therapy was begun with an initial dose of 50,000 units intravenously followed by 40,000 units intramuscularly every three hours thereafter. His general condition appeared to improve. The blood pressure did not fall, and the heart rate remained about 110 beats per minute. In the evening definite pitting edema of the lower arms and feet was present.

On the morning of the thirteenth day the blood pressure had dropped to 84 mm. Hg systolic and 48 mm. diastolic. The patient was comatose, and respirations were rapid and shallow. There were no changes in the lung signs from the previous day. The extremities were warm. The patient was given 600 c.c. of plasma intravenously, and rapid digitalization was begun. The blood pressure rose throughout the day to 110 mm. Hg systolic and 48 mm. diastolic in the afternoon. The electrocardiogram continued to show low voltage with T-waves of low amplitude in Leads I and II. Ventricular extrasystoles were no longer present. Cyanosis of the lips and nail beds continued. When the oxygen mask was removed for a few moments the radial pulses became weak and the cyanosis increased. The edema appeared to decrease slightly throughout the day. Aside from occasional twitching of the fingers no abnormal neurological signs were noted. In the early evening respirations became intermittent and ceased.

At postmortem examination important findings were the following: The rash was still present. The left ventricle was contracted. The cut surface of the myocardium was brownish in color. The dependent portions of the right and left lower lobes of the lungs were firm, dark red, and exuded thick yellowish exudate on pressure. The bronchial mucosa was intensely reddened. The spleen was enlarged to about twice its normal size and was soft in consistency. The right and left kidneys weighed 210 and 180 gm., respectively. Pin-point hemorrhagic spots were present on their surfaces and petechial hemorrhages were seen in the renal pelvises. The brain appeared grossly normal.

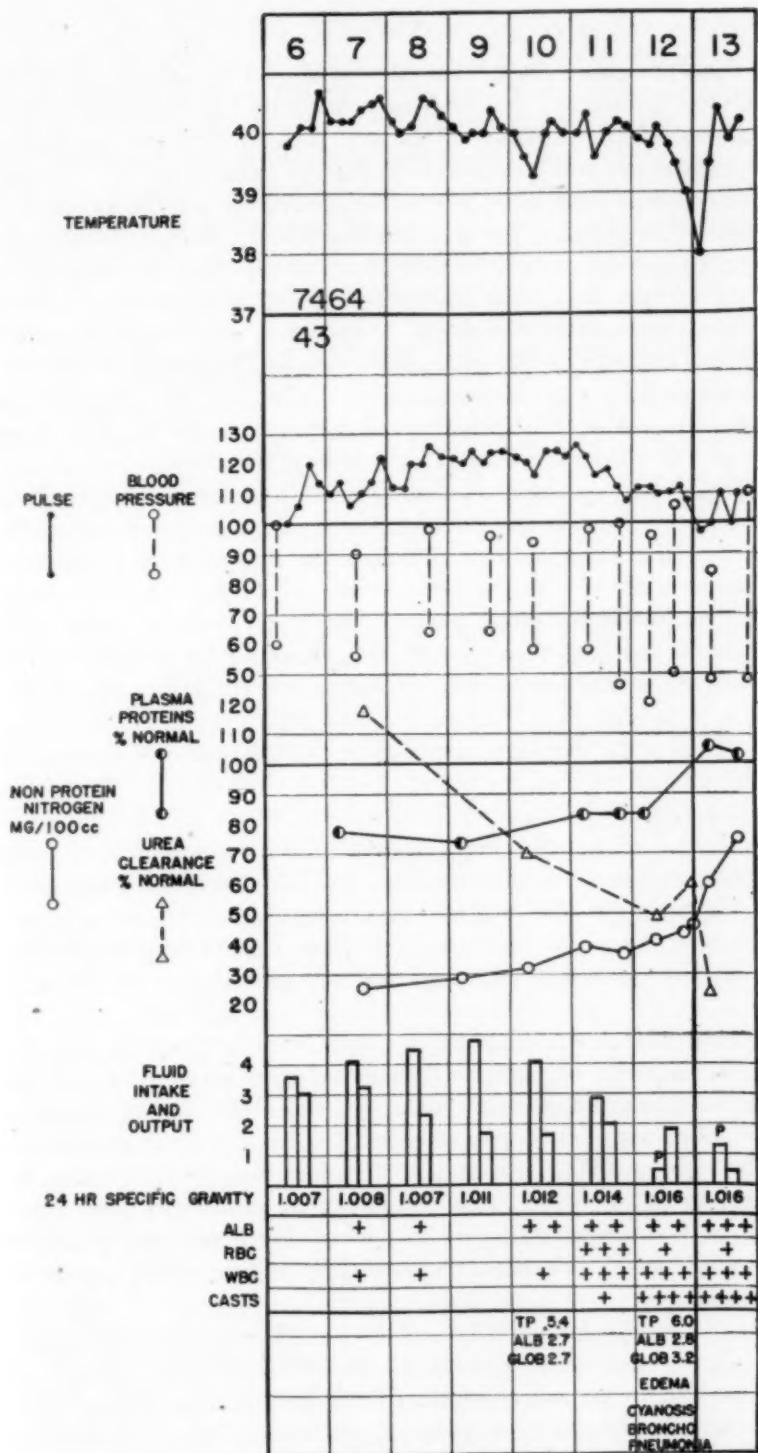


CHART 10. Case No. 7464.

## COMMENT

The data presented show that abnormal concentrations of blood non-protein nitrogen occurred in a high percentage of typhus patients during the febrile course of the disease. Azotemia was particularly frequent in the critically ill patients and a universal finding in fatal cases.

Additional information is needed to determine all the possible factors which may be responsible for the development of this condition in typhus. The observations obtained from this group of 64 cases, however, allow one to consider certain important phenomena which are present in this disease and appear to be associated with the development of nitrogen retention.

Since it is known that the greatest portion of the blood non-protein nitrogen is eliminated by way of the kidneys, the level of the blood non-protein nitrogen will rise when the formation of nitrogenous metabolites proceeds at a more rapid rate than the elimination of these metabolites in the urine. In certain febrile states associated with a great increase in protein catabolism the excretion of excessive amounts of non-protein nitrogen is dependent upon the existence of a urine volume sufficient for this purpose. When the volume of urine is reduced in the presence of one or more factors such as dehydration, or lowered arterial pressure, or when intrinsic renal damage is present with or without these factors, the excretion of non-protein nitrogen may be delayed to the point where abnormal concentrations are found in the blood.

The fundamental injury to the body in typhus is the widespread invasion of the endothelial cells of the blood vessels by rickettsiae. Thromboses of varying degree may follow such invasion and result in anoxemia and death of tissue cells. It appears certain that in the moderately or severely ill typhus patient considerable destruction of body protein takes place, particularly since the protein and caloric intake of the diet are almost always grossly insufficient. An increase in protein destruction under these conditions may be reflected in increased amounts of non-protein nitrogen in the urine.

Nitrogen balance studies were not done in this series of patients. The diet for the majority of patients during the acute phase of the disease consisted of water, sweetened fruit juice, and 600-1000 c.c. of whole milk per 24 hours. For example, during the first 16, 15, and 19 days of hospitalization patients No. 4690, 5508 and 5808 respectively, remained on this diet. It may be stated, therefore, that the intake of protein in these three cases, as well as in others, was far below that which is considered the minimum for normal individuals. Likewise, the total daily caloric intake was much lower than desirable.

A loss of weight between 15 and 30 pounds was the rule in severely ill patients during the febrile period of the disease. The patients observed were from the lowest social strata of the population. They were almost without exception lean men, with no excess fat when in good health. Under

these conditions it is probable that the great loss in weight which they experienced was due in most instances to the loss in body proteins.

Evidence obtained from the urea nitrogen values in urea clearance tests indicates that very large amounts of urea nitrogen alone must have been excreted by the kidney during the acute period of illness (table 6). In patient No. 5808, for example, large amounts of urea nitrogen were found in the urine on the fifteenth and nineteenth days of disease when the total caloric intake was almost entirely confined to parenteral 5 per cent dextrose in saline.

TABLE VI

The Estimated 24 Hour Output of Urine Urea Nitrogen in Typhus Fever; Based on Urine Urea Nitrogen Values Obtained during 2 Hour Urea Clearance Tests and Total Output of Urine during the 24 Hour Period

| Case No. | Day of Disease | Blood Urea Nitrogen<br>mg./100 c.c. | Urine Urea Nitrogen<br>gm./liter | Estimated 24 Hour Output of Urea Nitrogen<br>gm. |
|----------|----------------|-------------------------------------|----------------------------------|--|
| 4690     | 12             | 27                                  | 6.2                              | 7  |
|          | 14             | 57                                  | 8.1                              | 9  |
|          | 19             | 15                                  | 10.0                             | 11   |
| 5508     | 5              | 22                                  | 11.2                             | 17   |
|          | 7              | 17                                  | 6.7                              | 15   |
|          | 10             | 23                                  | 6.8                              | 19   |
|          | 14             | 20                                  | 6.1                              | 16   |
|          | 17             | 20                                  | 7.2                              | 24   |
| 5808     | 15             | 33                                  | 14.2                             | 16   |
|          | 19             | 16                                  | 7.7                              | 12   |
|          | 35             | 13                                  | 6.7                              | 13   |

Likewise, the estimated output of urea nitrogen in patient No. 5508 suggests that the excretion of total nitrogen must have been considerable, particularly in view of the very low protein intake (table 6). Although a loss of 21 pounds occurred in the first 14 days under observation in this case, nitrogen retention was minimal. This case illustrates the ability of some typhus patients to excrete large amounts of non-protein nitrogen with practically no rise in the blood urea nitrogen when the urine volume is above 2,000 c.c. daily.

As we have stated in the presentation of the data, azotemia appears to be closely associated with a decreased output of urine in cases which demonstrate efficient concentrating power of the kidneys by excreting urine with high specific gravities. The data on patient No. 5808 are illustrative. On the twelfth and thirteenth days of disease the fluid intake had decreased to little more than 1,000 c.c. in 24 hours. There was a simultaneous increase in urine concentration above 1.020. The blood non-protein nitrogen had not risen over 50 mg. per 100 c.c. after 48 hours of greatly reduced fluid intake in the presence of high fever. From the thirteenth to the eighteenth day of disease the fluid intake was almost entirely parenteral; the daily volume was small in amount. In the presence of a rising urine specific gravity there oc-

curred a rapid rise in blood non-protein nitrogen concentration. The urea clearance at that time was within normal limits. There then followed a decrease in blood urea nitrogen concentration with the decline in temperature to normal. The daily urine volumes, however, were still low and the specific gravities were high. This case illustrates the important probability that in the presence of good renal function a low output of urine may be responsible for azotemia in typhus. In such situations it appears that the low urine volume delays the excretion of excessive amounts of non-protein nitrogen with the result that high concentrations are found in the blood.

In contrast to the phenomena observed in patient No. 5808, there were other cases in which the daily urine volumes rarely exceeded 1500 c.c., but the specific gravities and urea clearances indicated a definite diminution in renal function. The data on cases No. 3307, 4690, 5133, 5769, and 7250 show that azotemia in these patients was associated with one important phenomenon which we have as yet not sufficiently considered. This was a rapid fall in arterial blood pressure.

Changes in renal function associated with changes in peripheral blood pressure<sup>37</sup> lead one to believe that significant changes in renal blood flow affecting renal function<sup>36</sup> might have been demonstrated in some or all of these cases if the newer methods<sup>38</sup> for the study of renal physiology in man had been utilized.

From the data on the five patients noted above the obvious phenomena associated with the presence or development of a low peripheral blood pressure were a decrease in the urine volume, urea clearance, and rise in the blood non-protein nitrogen. When observed, the fall in blood pressure occurred in the space of a few hours. It was of varying duration.

Another finding of importance which was common to these cases was the development of a urine specific gravity low in relation to the daily urine output. A state of renal insufficiency developed in these patients following the sudden fall in arterial pressure. This was characterized by a diminution in urine volume, a loss in concentrating power of varying degree, with a fall in urea clearance. The data indicate that the renal failure observed was at least initiated by extrarenal factors.

Although of serious prognostic import, this type of renal failure was not always progressive, even in cases which terminated fatally. Cases No. 3307 and 5769 showed a tendency for renal function to improve in the final days of life. In most cases renal failure did not improve and was associated with rapid death, as exemplified by cases No. 5133, 6146, and 7250.

A few patients who developed this type of renal failure recovered from typhus. The sequence of events outlined on the chart of patient No. 4690 was quite characteristic for this small group. With the rise in blood pressure there was an associated return of renal function with a fall in the blood non-protein nitrogen. The supportive treatment of such cases did not differ in any way from that employed in cases which developed renal insufficiency and later died.

Although the majority of fatal cases appeared to develop renal insufficiency preceded by a rapid fall in blood pressure, there were rare cases observed in which this factor was not seen. The data on patient No. 7464, for example, suggest that renal insufficiency developed several days before death in the absence of a fall in blood pressure or increasing dehydration. It cannot be denied, however, that the blood pressure during hospitalization in this patient may have been much lower than before he came under observation. It may be, nevertheless, that an overwhelming rickettsial infection, such as this patient demonstrated clinically, affects renal function through mechanisms which are at present unrecognized. The possible direct effect of rickettsial toxic substances upon the kidney, for example, is unknown.

A discussion of the possible causes for the rapid fall in arterial pressure is beyond the scope of this paper. Recent studies have been made concerning alterations in the cardiovascular system in typhus.<sup>2, 15, 18, 19</sup> Our studies of the cardiovascular changes associated with this disease are still in progress and will be reported in a later communication.

One of our cases merits special attention since the course of events in this man's illness was unique in our experience with typhus. Patient No. 1109, an "E" case, showed evidences of severe renal insufficiency throughout his hospital course. The urine specific gravity remained relatively fixed in spite of large fluctuations in the daily output. Increasing dehydration was neither in evidence clinically nor by observation of the plasma protein levels. After the first hospital day his diastolic blood pressure remained consistently elevated for 16 days. He developed an anemia of far greater severity than is usually seen in typhus, together with edema and hypoproteinemia. Serial electrocardiograms showed evidence of extensive myocardial changes. Numerous red cells and red cell casts appeared in the urine during the fourth week of his illness. His convalescence was complicated by otitis media and erysipelas. Follow-up examinations over a nine month period showed consistently diminished concentrating power of his kidneys with albuminuria, occasional red cells, white cells, granular and hyaline casts. His basal diastolic blood pressure was elevated at times to 90 mm. of mercury. The red blood cell count returned to normal but the electrocardiograms remained persistently abnormal.

The diastolic blood pressure levels present during the acute phase of this patient's disease have so far not been observed by us in any other severe case of typhus. A diastolic level of between 86 mm. and 90 mm. of mercury in severe typhus constitutes a relative hypertension which is not without significance. The specific gravity of the 24 hour urine samples, furthermore, suggests that the degree of nitrogen retention found was dependent upon renal failure rather than on deficient fluid intake in the presence of good renal function. The phenomena observed in this case may be explained either by assuming that this patient had considerable hypertension before

the onset of typhus, with a relatively severe drop in blood pressure during the disease,—a theory not upheld by subsequent studies in this case since the blood pressure was not found greatly elevated at any time during the follow-up examinations—or that the course of typhus fever was associated with an acute nephritis. In this regard one may speculate whether or not latent nephritis was present before the onset of typhus. No history of previous headaches, edema, or abnormal appearance of the urine was obtainable. However, there was evidence in the form of persistent albuminuria and diminution in the concentrating power of the kidneys to confirm the belief that residual renal damage was still present. In view of our experience to date that severe renal insufficiency in typhus is closely associated with extrarenal factors and has never yet been shown conclusively to produce persistent renal damage in cases which recover, we believe this patient most probably had chronic renal disease with an acute exacerbation during the course of typhus. The electrocardiographic changes which persisted for almost a year after the disease are unique in our experience, and indicate that extensive involvement of the heart was present during the acute phase of typhus resulting in permanent myocardial changes.

In concluding the comment on the data presented we can state that our studies have so far indicated that the development of nitrogen retention in this disease is the result of a number of factors which may be more often encountered in typhus than in other acute infectious diseases.

To begin with, the circumstances under which epidemic louse-borne typhus occurs and is observed impose a fundamental consideration in the concept of the origin of azotemia in this disease, namely, that the caloric and protein intake of nearly all typhus patients is grossly insufficient. There is good reason to believe that the destruction of the body tissues must be considerable. As a result of such tissue destruction, the elimination of large amounts of non-protein nitrogen is dependent upon a larger daily volume of urine than would otherwise be necessary if protein catabolism were proceeding at a more normal rate. In order to prevent the accumulation of nitrogenous metabolites in the blood, the excretion of an adequate output of urine for this purpose is necessary. In the presence of greatly increased protein catabolism it is apparent that dehydration with a diminished output of urine will have considerable effect upon the degree of azotemia observed.

Another factor closely associated with the development of azotemia in typhus is encountered in the more critically ill patients and is of the greatest importance. This is the onset of renal insufficiency, most often associated with a rapid fall in blood pressure. The renal insufficiency met with in these patients is of serious prognostic import. In our experience the patients who have survived have been very few in number. We do not imply that the cause of death in such cases is renal failure. The majority of these patients died with evidences of overwhelming rickettsial infection or complicating conditions such as pneumonia. Nevertheless, a rapid diminution in kidney

function was almost without exception the first indication that the patient would probably succumb to the disease. The presence of renal insufficiency itself was of more significance than a fall in blood pressure, since at times such a fall was not observed or occurred in the absence of renal failure. At present we have no evidence to indicate that the loss of renal function observed in these critically ill patients was due to other than extrarenal factors.

In addition to deficient total caloric intake and tissue protein destruction, dehydration, and the rapid development of renal insufficiency in typhus, there may be other factors which are important in the production of azotemia in this disease. As yet we lack important data on the type of circulatory failure which may be present in some patients, as well as alterations in electrolyte balance, renal blood flow, and pathologic histologic changes in the kidney, which may be found in cases similar to those cited in this paper. Obviously, much additional information is needed before all the phenomena which may contribute to the development of azotemia in typhus are well understood.

#### SUMMARY AND CONCLUSIONS

The experience with "untreated," unvaccinated typhus fever patients during two epidemic years has been analyzed with reference to the incidence of nitrogen retention and to certain factors which may contribute to its development. The data were obtained from 64 patients on the United States of America Typhus Commission ward and 14 patients on the general wards of the Cairo Fever Hospital.

Azotemia in epidemic louse-borne typhus fever was found to occur very frequently (in 52 per cent of the cases), as indicated by elevated concentrations of blood non-protein nitrogen, urea nitrogen, and creatinine.

The correlation between clinical severity and azotemia was striking. Elevated concentrations of blood non-protein nitrogen were found in every fatal case whose blood was examined.

This phenomenon was not restricted to older age groups. With one exception positive evidence for glomerular nephritis was lacking in all cases in which the urine was frequently examined. Follow-up examinations over a period of months have shown no impairment of renal function in even the most critically ill patients with severe renal insufficiency, except in rare instances in which the possibility exists that renal disease was present before the onset of typhus.

In this series of typhus cases azotemia appeared to be closely associated with excessive destruction of body protein and increased nitrogen excretion, with dehydration and a reduced output of urine in the presence of normal kidney function, and in severe cases with a sudden rapid fall in blood pressure associated with evidences of renal insufficiency.

The appearance of renal insufficiency as a complicating condition in the disease was in nearly every instance the earliest indication that the patient's course would be very severe or would end fatally.

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## OBSERVATIONS ON THE TREATMENT OF GRAVES' DISEASE WITH THIOURACIL \*

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OVER two years have elapsed since Astwood<sup>1</sup> first reported his observations on the use of thiouracil in a patient with thyrotoxicosis. It is now well known that the drug has a remarkable effect in preventing the formation of thyroid hormone and that its clinical use may cause striking improvement in the symptoms of Graves' disease. Unfortunately experience has also shown that the drug possesses some serious toxic properties and especially a tendency to cause granulocytopenia or even fatal agranulocytosis. It is not yet established whether it is safe for general use, whether under any circumstances its use constitutes a permanent cure or to what extent it may be regarded as a substitute for surgery. These are questions which can be answered only by extensive clinical trial. The drug is being widely studied, and numerous reports of its use have appeared in the recent literature.

Our experience with thiouracil at New York Hospital has accumulated since September 1943, and during the intervening 21 months a study has been made of 100 cases of hyperthyroidism. These included all thyrotoxic patients who were admitted to the medical wards during the period, three from the surgical service, five from the private practice of members of the staff, and two cases of mild Graves' disease who were treated ambulantly in the out-patient department.

Since patients entering the medical wards were taken without selection, the experience has been varied, and includes many of the vicissitudes which are likely to be encountered in the use of the drug. Some of the data concerning those who were treated are presented in table 1. Severe, mild and recurrent cases were included in the series. The majority of the goiters were classified as diffusely hyperplastic but there were many frankly nodular glands. The size varied greatly from several which could not be palpated by clinical examination to one huge, irregularly nodular goiter which compressed the veins of the neck and hung over the clavicles and sternum. Some of the patients had symptoms of very recent origin. One man had had the manifestations of Graves' disease for at least 25 years. Complicating conditions were numerous and included coronary and rheumatic heart disease, peripheral vascular disease, bronchiectasis, epilepsy, nephrolithiasis, and several psychoneuroses.

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## CIRCUMSTANCES OF THE STUDY

*Hospitalization.* With two exceptions treatment during the intensive use of thiouracil was carried out in the hospital. Hospitalization was regarded as desirable because of the possibility of insidious development of toxicity, which might be recognizable only through close clinical observation and the prompt use of laboratory aids. It also served to make studies of clinical and chemical changes more inclusive than could be accomplished easily in the out-patient department. Several of the patients were intensively

TABLE I

|  |     |
|--|-----|
| Total Number of Cases Exposed to Thiouracil.....                                 | 100 |
| Time under Observation   |     |
| For 24 months.....   | 2   |
| over 18 months.....  | 13  |
| over 12 months.....  | 26  |
| over 6 months.....   | 29  |
| less than 2 months.....  | 8   |
| Age  |     |
| varied from 15 to 68 years   |     |
| Sex  |     |
| Women.....   | 80  |
| Men.....   | 20  |
| Duration of Illness  |     |
| 6 weeks to 25 years  |     |
| Severity of Disease  |     |
| B.M.R. varied from +2 to +72   |     |
| Only 4 cases treated with initial B.M.R. below +20                               |     |
| Previous Use of Iodine   |     |
| 19 patients were known to have received iodine up to time thiouracil was started |     |
| Previous Thyroidectomy   |     |
| 2 patients had had 3 operations  |     |
| 1 patient had had 2 operations   |     |
| 4 patients had had 1 operation   |     |
| Type of Goiter   |     |
| Series included both diffusely hyperplastic and nodular goiters.                 |     |

studied in the metabolism ward of the Russell Sage Institute of Pathology. In those treated on the wards of the medical service a routine was established by which a variety of preliminary observations was obtained. The basal metabolic rate was determined before treatment often enough to establish a control level. The greatest circumference of the neck was recorded and careful exophthalmometric measurements were taken with the Hertl exophthalmometer. In addition to record of the pulse rate and blood pressure, the circulation rate was obtained by the use of decholin. Venous pressures were measured whenever the initial venous pressure appeared to be elevated. In many cases there were studies of cholesterol content of the serum, creatinine excretion, spontaneous creatinuria, and creatine tolerance. In a few cases sugar tolerance tests were made. Chemical tests for blood sugar, blood urea nitrogen, total protein, albumin-globulin ratio, calcium, phosphorus, and phosphatase in the serum were made routinely. All of these tests and measurements were repeated during or at the end of the intensive therapy before the patient was discharged from the hospital. In addition, white blood cell and differential counts were made at one to two day intervals.

In all but the earliest cases, icterus indices and prothrombin times were determined with the idea of detecting any possible hepatic damage.

*Dosage of Thiouracil.* The dosage of the drug varied. In the earliest cases 0.8 gm. was given daily in divided doses. When beneficial effects were delayed, the dose was increased to 1.0 or to 1.2 gm. and in one instance to 2.0 gm. daily. Later, and in the majority of cases here reported, 0.6 gm. of thiouracil was given during the day in 6 doses of 0.1 gm. each. Such intensive therapy was continued until the basal metabolic rate had attained normal levels. From review of the data it was not apparent that larger doses were more effective than 0.6 gm. daily. For maintenance of effect 0.1 to 0.2 gm. was given each day after the patient left the hospital.

*Use of Iodine.* Except in two cases, iodine was not prescribed during the period of intensive thiouracil treatment until the basal metabolic rate had attained a normal level or until (in two cases) it was apparent that thiouracil was not benefiting the patients. During maintenance treatment with thiouracil iodine in the form of syrup of hydriodic acid 1.0 c.c. each day was often added.

## RESULTS

In 89 of the 100 cases exposed to the drug, treatment was completed in the sense that it was continued long enough to judge its effectiveness. Success was estimated by the return of the basal metabolic rate to normal levels and by satisfactory control of other manifestations of the disease. By these criteria there were 87 successes and two failures. Two patients died of cardiac complications during the period of intensive treatment. In nine of the 100 cases intensive treatment with thiouracil was abandoned because of unfavorable reactions which were or might have been attributable to the drug.

*Failures.* The two cases classified as failures are of considerable interest.

R. B., an intense Italian woman, aged 49, was said to have had a basal metabolic rate of +100 before admission. She had received no iodine or other medication for the control of her thyrotoxicosis. The first basal metabolic rate on the ward was +83. Three days later it was only +36 but on the day before treatment was started it rose to +52. She received 0.6 gm. of thiouracil for 15 days, 0.8 for 8 days, 1.2 gm. for 14 days. At the end of 40 days her basal metabolic rate was still +56. She had gained no weight and the symptoms of thyrotoxicosis continued to be disturbingly severe. Thiouracil was continued and a daily dose of 1.0 c.c. of syrup of hydriodic acid was added. Five days later her basal metabolic rate was +61. She was transferred to the surgical ward where the basal metabolic rate was not materially influenced by discontinuance of thiouracil and hydriodic acid or by exhibition of larger doses of iodine (1.8 c.c. of Lugol's solution daily). In spite of her unfavorable condition, subtotal thyroidectomy was performed and was followed by an uneventful convalescence. Contributory factors to failure may have been worry about money, worry about eight children, and a large nodular goiter. Since there was no digestive disturbance it seemed unlikely that the lack of therapeutic effect could be attributed to a fault in absorption of the drug.

O. B. was a worrisome, anxious woman of 44 who had serious hypertension as well as thyrotoxicosis. The hyperthyroidism had been recognized for four months. She had taken iodine until the time of her admission to New York Hospital. It was estimated that her thyroid gland was about six times normal size. The basal metabolic rate before treatment varied between +33 and +28. Treatment with thiouracil accomplished no obvious improvement. At the end of 28 days, her basal metabolic rate had risen to +40, her weight was essentially unchanged and symptoms of thyrotoxicosis were increasing. She was transferred to the surgical service where iodine was added to her treatment. After 28 days of thiouracil and 13 days of iodine and thiouracil her condition was not improved. Thyroidectomy was performed without untoward symptoms. Factors contributing to failure may have been previous iodination, the large size of the gland, hypertension and the patient's inability to adapt herself to her illness or her environment. No fault in absorption was apparent.

*Factors Influencing the Rate of Response.* It was arbitrarily decided to discontinue intensive therapy when the basal metabolic rates had fallen to a range of between +15 and -10. The rapidity with which normal levels were attained varied between four and 108 days from the beginning of therapy. Beneficial effects of the drug were usually apparent within the first 10 days and by the fortieth day, the basal metabolic rate had returned to normal levels in over 80 per cent of the cases.

*Severity of Thyrotoxicosis.* Factors influencing the rate of recovery were only partially evaluated. In general it appeared that the degree of initial thyrotoxicosis was not a reliable criterion. Although some of the most dramatic and satisfactory responses to the drug occurred in patients whose initial basal metabolic rates were greatly elevated, there were two with initial rates above +60 who required more than 60 days to attain normal levels.

*Size of Goiter.* The size and character of the thyroid gland appeared to have some significance. The longest delays were encountered in cases with large nodular goiters. More often than not, response was prompt in patients who had small, diffusely hyperplastic glands. It was thought that this correlation might depend upon the amount of thyroid hormone which had been stored in the gland previous to the exhibition of thiouracil. Relative depletion of thyroxin might be expected in some of the small and very active glands whereas large and nodular goiters might have stored a large amount.

*Previous Iodine Medication.* Response to thiouracil was on the average less prompt in those who had taken iodine in the immediately preceding period. More than one appeared to become somewhat worse for a time after iodine was discontinued and thiouracil started. One patient, Be, who came to the metabolism ward in an extreme state of thyrotoxicosis after nine months of iodine had a very prompt response to thiouracil. This was not an isolated example. On the other hand in the following patient who responded most satisfactorily to iodine, there was a considerable delay in the benefit from thiouracil.

J. M., a married woman of 32, was purposely given iodine in the form of 1.0 c.c. hydriodic acid each day for a period of two weeks. The iodine was then withdrawn

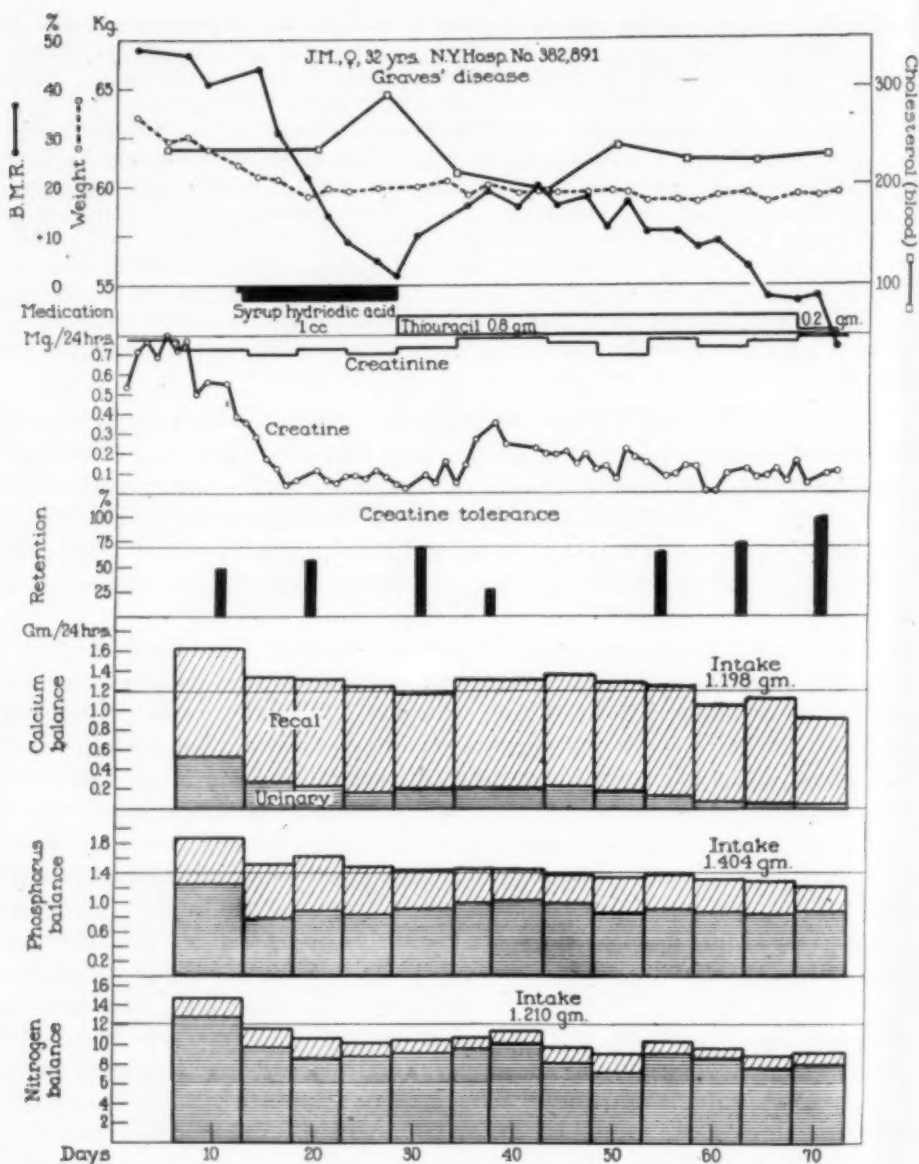


FIG. 1. Chart of J. M. showing metabolic changes during the use of iodine and the later use of thiouracil.

and thiouracil in daily doses of 0.8 gm. was substituted. Progress was carefully observed in the metabolism ward. It will be seen in figure 1 that the response to iodine was prompt in terms of its effect on the basal metabolic rate as well as on the creatine metabolism. When, however, iodine was withdrawn there was a prompt release of iodine effect, with moderate relapse, indicated by rise in spontaneous creatinuria, diminution in creatine tolerance and elevation of basal metabolic rate. Actually 20 days elapsed, before the benefits of thiouracil were apparent, and more than 30

were required before the condition became as favorable as it had been when the iodine was discontinued.

It is clear in this case that the benefit of iodine was lost before the action of thiouracil was established. The observations suggest also that for optimum control in this patient iodine should have been continued during the first few weeks of thiouracil treatment.

Perhaps the effect of preceding iodine medication upon the response to thiouracil depends upon its influence on the storage of thyroxin in the thyroid gland. This in turn is generally although not invariably related to the effect of iodination on thyrotoxic symptoms and the basal metabolic rate. It might be expected, therefore, that the more effective the previous iodination had been, the greater the likelihood of thyroid hormone storage and of delay in thiouracil effect. Thus, Be, who was uncontrolled by iodine manifested a very rapid response to the drug whereas in Ma, who had had remarkable improvement under iodine medication, the effect of thiouracil was delayed.

#### EFFECTS ON SYMPTOMS AND SIGNS OF THYROTOXICÖSIS

*Weight.* The emaciation of thyrotoxicosis was in most instances easily corrected. Two patients lost respectively 0.5 and 1.5 kg. during the course of the treatment. In a few cases the weight remained stationary. Usually there was a striking gain often beginning after the first few days of treatment. Gains of from 5 to 10 kg. were frequent. In one patient the weight increased 12.5 kg. during two months of intensive therapy. Neither this nor other large gains in weight could be attributed to edema.

*Size and Character of the Gland.* Because early observations in animals had demonstrated hyperplasia,<sup>2,3</sup> it was expected that beneficial action of the drug might be accompanied by demonstrable enlargement of the thyroid. Routine measurements during the period of intensive therapy failed to reveal important changes. The significance of slight variations was made less clear by gains in weight which might have been sufficient to increase the girth of the neck without enlargement of the gland. In no case during intensive therapy was there any change in size which could be regarded as disadvantageous to the patient. During the course of maintenance therapy, the gland in two patients increased in size and in one to such a degree that operation was thought to be necessary. Postoperative examination revealed an involuted gland with no suggestion of carcinoma and with few areas of hyperplasia. Thiouracil did not increase the firmness of the gland. Bruit and thrill if present before treatment were not diminished. In some cases the bruit increased in intensity and was loudest after most of the other signs of hyperthyroidism had disappeared. Gradually during maintenance therapy the bruit tended to disappear. In these cases administration of iodine without discontinuance of thiouracil caused increase in firmness of the gland and rapid subsidence of the bruit.

*Exophthalmos.* Observations on the eyes of patients treated with thiouracil were of great interest. It was suspected that thiouracil might increase the degree of protrusion of the eyeballs not only because of the case of malignant exophthalmos encountered by Williams<sup>4</sup> but also because of the well attested facts that pituitary thyrotropic hormone tends to cause exophthalmos and that diminution in circulating thyroid hormone such as occurs during thiouracil therapy stimulates the production of thyrotropic hormone.

In none of the patients was there evidence that thiouracil diminished the protrusion of the eyeballs. On the contrary actual measurements indicated in some cases a recognizable increase in prominence. Although this seldom amounted to more than 2 mm. on the Hertl exophthalmometer the increase in one case was as much as 4 mm. In no instance was the protrusion sufficiently great to cause troublesome symptoms, nor did the continuation of the drug ever result in progressive exophthalmos.

Although protrusion of the eyeballs was not favorably affected, spasm of the eyelids and the concomitant lid lag were diminished and in most of the cases entirely abolished. This led to the clinical impression that the exophthalmos had been greatly improved by the treatment and from a functional standpoint this was true. In one patient, who before treatment had extreme exophthalmos with bilateral corneal ulceration, the relaxation of lid spasm by thiouracil was apparently determinant in return of effective coverage by the lids and by the disappearance of corneal lesions.

The effects of thiouracil on eye symptoms are approximately those which have been observed following subtotal thyroidectomy. Recent careful exophthalmometry has demonstrated that protrusion of the eyeball tends to increase moderately following operation and that the improvement in eye symptoms long ascribed to surgery consists almost entirely in the control of lid spasm.<sup>5</sup>

*Effect on Tremor and Hyperkinesis.* The fine intense tremor was promptly diminished by thiouracil and in most instances was entirely abolished. One of the most striking effects of the drug appeared in the elimination of the purposeless movements which are so characteristic of the thyrotoxic state. Even patients who before treatment had exhibited choreiform speech and athetoid motions rapidly attained a state in which the physical effects of emotion seemed actually less than normal.

*Circulatory Disturbances.* In many patients, tachycardia and fall in both systolic blood pressure and pulse pressure paralleled the diminution in basal metabolic rate. This was by no means constant and some continued to display highly variable degrees of tachycardia and definitely elevated pulse pressure long after other symptoms of the disease had become quiescent. Palpitation as a symptom tended to disappear as the thyrotoxicosis subsided. Circulation rates increased to normal in patients whose hearts were not initially decompensated. Although the tendency was always toward improvement it can be said in general, however, that the circulatory phenomena

were too variable to offer reliable criteria of the effectiveness of the drug or of the degree of benefit to be derived from its use.

Several patients in the group had cardiac arrhythmias and a few had serious rheumatic or coronary heart disease before treatment was started. No reversion of auricular fibrillation to normal rhythm could be attributed to therapy. One case of paroxysmal auricular flutter was entirely relieved of her attacks under the influence of thiouracil.

There were three deaths from cardiac disease during the course of treatment.

*Mc*, a man of 62 with arteriosclerotic heart disease and thyrotoxicosis, died of coronary occlusion during intensive therapy. On the second day of treatment with thiouracil he had a febrile reaction the cause of which was not determined but which led to discontinuance of the drug. A test dose of 0.1 gm. 15 days later was followed by no fever or other unfavorable reaction and after an interval of five days he was started on daily doses of 0.8 gm. of thiouracil. Three days later he died. Autopsy revealed evidences of atypical coronary occlusion.

*Me*, a married woman of 28, had been known to have rheumatic heart disease with involvement of both aortic and mitral valves for many years before onset of thyrotoxicosis. Hyperthyroidism was easily controlled with thiouracil. During maintenance therapy, however, there developed increasing signs of heart failure which were imperfectly controlled by digitalis, mercupurin and rest. She died of cardiac decompensation five months after thiouracil treatment had been instituted. No autopsy was obtained.

The third patient who died of circulatory failure presented a complicated picture of disease which requires analysis and comment.

*Sh* was a woman of 60 who had suffered for four years from angina pectoris associated with hypertensive cardiovascular disease. For an undetermined period she had had an asymptomatic nodular goiter. She had also been correctly diagnosed and treated as a case of pernicious anemia. During routine treatment in the hematology clinic the basal metabolic rate was found to be +44 and she was admitted to the hospital. At that time she had severe anginal pain and shortly thereafter developed auricular fibrillation with increasing heart failure. She was treated with rest, digitalis and mercupurin and after 22 days had partially recovered compensation. It was at this time that thiouracil treatment was started. On the ninth day she developed fever with vomiting. The drug was discontinued. After an interval of 17 days she was given a test dose of thiouracil and since there was no reaction the drug was started again, in daily doses of 0.6 gm. Three days later she died suddenly. Autopsy revealed slight if any hypertrophy of the heart. There was, however, an extensive acute myocardial reaction with necrotizing coronary arteritis and periarteritis. The vessels themselves were not significantly thickened and there was no great amount of fibrous tissue in the myocardium but in many areas adjacent strands of muscle were separated by areolar tissue in which there was invasion of eosinophiles, polymorphonuclear leukocytes and histiocytes with a smaller number of lymphocytes. These changes were thought to be not unlike those found by Rich<sup>6</sup> in rabbits rendered sensitive to horse serum.

In evaluating this case it is perhaps important to emphasize that preceding thiouracil treatment there was a history of pernicious anemia and long standing angina pectoris and recent onset of auricular fibrillation and increas-

ing cardiac decompensation. This background suggests that death was attributable to causes other than thiouracil. The possibility cannot be excluded, however, that the acute myocardial lesions were caused by a sensitivity to the drug. This incident which occurred early in the use of the drug made us observe even more carefully the behavior of all patients under treatment with thiouracil and particularly of those having signs of cardiac disease.

*Serum Cholesterol.* Initial levels of serum cholesterol in these thyrotoxic patients tended to be lower than normal although they were in themselves seldom diagnostic. Improvement in clinical symptoms and return of basal metabolic rate to normal levels was with an occasional exception as in J. M. in figure 1 accompanied by a corresponding elevation in cholesterol values. Determination of cholesterol, moreover, was found to be helpful in recognizing the onset of myxedema. An example of this may be seen in figure 2 where the cholesterol continues to rise while the basal metabolic rate remains stationary. In another case there were early symptoms of hypothyroidism at a time when the basal metabolic rate was still above normal. Two weeks later when the patient presented myxedematous swelling, changed voice, falling hair and dry skin the basal metabolic rate was still +14 but cholesterol was 433 mg. per cent. In still another case of hypothyroidism induced by thiouracil it was found that the cholesterol values returned to normal coincident with the restoration of normal clinical behavior but at an interval of six weeks before a normal basal metabolic rate had been attained.

*Creatine Metabolism.* Muscular weakness and defects in creatine metabolism are among the most constant manifestations of thyrotoxicosis. In only a few of the patients in this series was weakness extreme, but in all who were tested there was abnormality in creatine metabolism as shown by excessive spontaneous creatinuria, a reduced creatinine excretion and a diminished creatine retention after a test dose (1.32 gm.). The character of the creatine defect and its prompt correction by thiouracil are shown in figure 2, which exhibits creatine and creatinine excretion as well as creatine tolerance tests before and after treatment.<sup>7</sup> In this case as in others similarly studied changes in creatine metabolism reflected benefit more promptly than did the basal metabolic rate or other criteria of improvement.

*Excretion of Nitrogen, Calcium and Phosphorus.* Characteristic of thyrotoxicosis is a tendency to constant or intermittent excessive loss of nitrogen, calcium and phosphorus. Studies portrayed in figures 1 and 2 indicate the effect of thiouracil in reducing urinary and fecal excretion of all of these substances.

*Other Functions.* Of the many tests performed routinely only a few revealed data of significance. Levels of blood urea nitrogen, total protein, albumin, globulin, calcium, phosphorus and alkaline phosphatase were unchanged by the drug. On the other hand the glycosuria of hyperthyroidism tended to disappear and the trend toward improvement was indicated in a

number of cases by lower glucose tolerance curves in the period after the drug had been given. One patient, a woman of 68, who had been taking 30 units of protamine insulin, was maintained without insulin, without dietary restriction, and with only occasional glycosuria for several weeks during

### Effects of Thiouracil on Graves' Disease Metabolic Effects

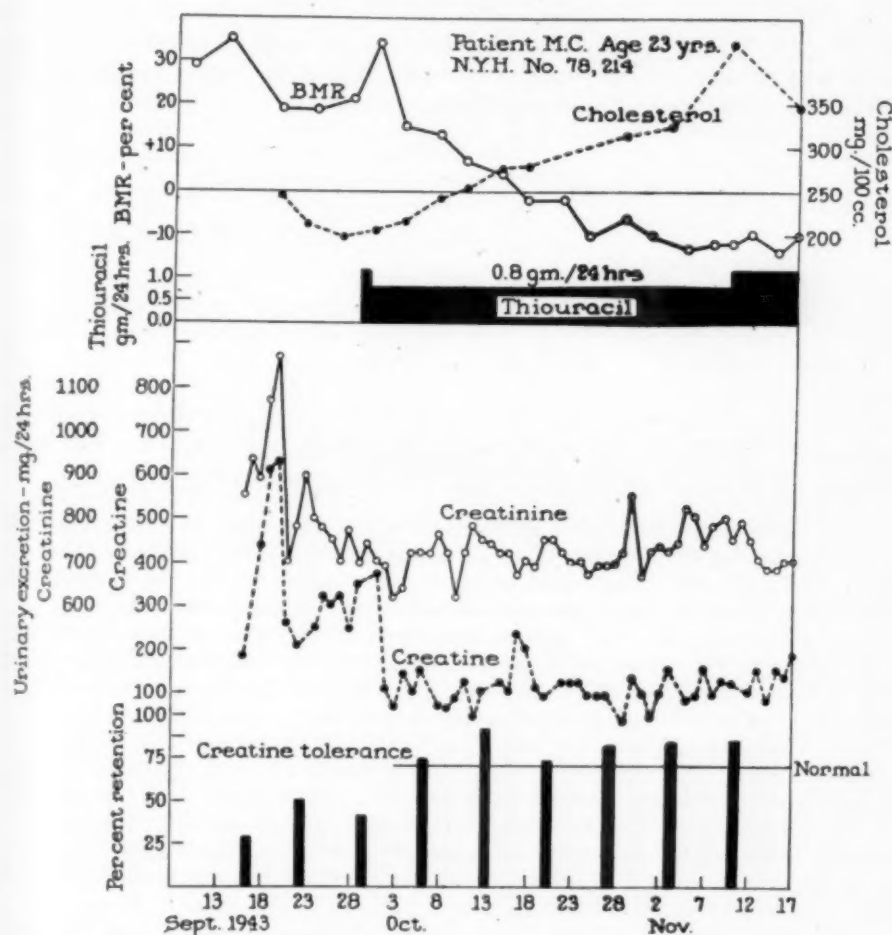


FIG. 2. Chart of M. C. showing metabolic changes accompanying the use of thiouracil.

intensive treatment with thiouracil. Later, however, massive glycosuria reappeared and during maintenance therapy insulin again became necessary for the control of a true diabetes.

**Behavior.** In the majority of cases thiouracil accomplished a most profound transformation in the psychological state of thyrotoxic patients. Their agitation, their restless striving and their exaggerated reaction to

minor stimuli were replaced by a calm demeanor which at times appeared to be almost abnormal. Life situations which previously had caused them great perturbation or distress were accepted with philosophical composure. Their behavior seemed to suggest that under the influence of the drug some mechanism for usual emotional responses had been dulled or lost. A tendency of this kind was noted in many patients who did not display other evidences of hypothyroidism.

*Toxicity.* All of the unfavorable reactions which developed in 100 cases treated with thiouracil are listed in table 2. In many instances great difficulty was encountered in deciding whether or not the untoward symptoms could be fairly attributed to the drug.

TABLE II  
Unfavorable or Toxic Reactions to Thiouracil

|                          |   |
|--------------------------|---|
| Eruptions.....           | 8 |
| Fever.....               | 4 |
| Conjunctivitis.....      | 2 |
| Leukopenia.....          | 8 |
| Thrombocytopenia.....    | 1 |
| Nausea and vomiting..... | 1 |
| Jaundice.....            | 1 |
| Hematuria.....           | 1 |

*Eruptions.* Erythematous, urticarial, and purpuric eruptions were encountered. The following abstracts illustrate the range of the lesions. The etiological rôle of thiouracil in the first four cases seems doubtful.

*Fo.* Itching, red, punctate eruption over the abdomen occurred at the end of the first week of 0.4 to 0.6 gm. daily doses of thiouracil. The drug was discontinued and iodine was substituted. There were no observations to substantiate the causative rôle of the drug. Subtotal thyroidectomy was performed on the twenty-fifth day.

*Ja.* Urticaria which had been troublesome for several weeks before thiouracil treatment continued intermittently and irregularly after the drug was started. On two occasions administration of thiouracil during an interval free of urticaria was followed by an attack. During initial intensive treatment (0.4 to 0.8 gm. daily) for 17 days, however, urticaria was not notably worse than it had been on occasions previous to the exhibition of the drug. After discharge from the hospital, giant urticaria developed during a period when iodine was substituted for thiouracil.

*Mi.* Urticaria developed on the twenty-first day of treatment. Skin tests were negative to thiouracil. There was no recurrence for several weeks after resumption of the drug. A subsequent attack subsided when thiouracil was withdrawn but did not recur with resumption of treatment.

*She,* a woman of 25, received thiouracil in daily doses of 0.6 gm. On the fourth or fifth day of treatment she noted a few small papules, thickly dispersed over the thighs. At first this was thought to be ascribable to the drug but it was later found that its inception corresponded exactly with the first use of freshly laundered hospital pajama pants. Discontinuance of this apparel resulted in prompt disappearance of the eruption.

In the next two eruptions thiouracil appeared to be the causative agent.

*Ho.* Fever and eruption developed on the tenth day of thiouracil treatment. The drug which had been administered in daily doses of 0.8 gm. was discontinued. After

an interval of four days, it was again given, for two days in doses of 0.2 gm. and for three days in doses of 0.4 gm. An eruption with edema then developed and terminated the therapeutic trial. A week later subtotal thyroidectomy was performed without incident.

*Ku*, a woman of 55 who had had two previous thyroidectomies, responded promptly to thiouracil and was maintained on 0.1 gm. daily for a period of four months. She then began to complain of pains in her legs. A few days later an eruption was noted on the legs. The lesions were discrete, nodular, tender, slightly erythematous and extended over both anterior and posterior surfaces below the knees. They were exaggerated by standing or walking but did not disappear over a period of six weeks. Clinically they resembled erythema nodosum. Biopsy revealed no distinctive pathological features. At first the lesions were not ascribed to thiouracil. Finally, however, the drug was discontinued. The eruption gradually subsided but returned promptly with a test dose of 0.1 gm. of thiouracil. The drug was withdrawn and subtotal thyroidectomy was performed.

The difficulty of judging the rôle of the drug in causation of eruptions is well illustrated by the following cases.

*Ra*. On the third day of treatment an erythematous eruption accompanied by 5 per cent eosinophilia occurred on the extensor surfaces of the arms and the flexor surfaces of the legs. Since this had not faded or changed after five days the drug was discontinued. In three days the rash had disappeared. Careful skin tests showed no local reaction to thiouracil. A test dose of 0.1 gm. was then given since no unfavorable symptoms developed. A test dose of 0.2 gm. caused no eruption. Intensive treatment with 0.6 gm. daily was reinstituted and continued for 17 days, without untoward event. The eruption then reappeared. The drug was withdrawn for three days but when the rash faded was again given in dosage of 0.6 gm. until the hyperthyroidism was entirely controlled. Maintenance therapy was continued for six months thereafter. During this entire period there were no dermatological manifestations.

*Ch*. An anxious excitable woman of 27 had with thiouracil therapy a satisfactory remission which was maintained on doses of 0.1 gm. for a period of four months. At the end of this time she suffered a partial relapse which was controlled by increasing the dose to 0.2 gm. Two months after starting the larger dosage a purpuric eruption was noted. This was greatest on the legs but was also seen as a few discrete patches on the arms. It continued for five days before thiouracil was withdrawn. In three days the eruption had faded. She then took phenobarbital for sleeping and the following morning the eruption had reappeared. Thiouracil was started again in doses of 0.1 gm. four times daily and was continued for three days without event. Then a leukopenia of 3,000 without granulocytopenia and with sharp increase in immature granulocytes was noted and the drug was withdrawn. Later a test dose of 0.1 gm. of thiouracil caused no symptoms but 0.2 gm. was followed promptly by reappearance of purpuric eruption. With this there was a slight fall in leukocytes without granulocytopenia. Subtotal thyroidectomy was advised. Test doses of 0.1 and 0.2 gm. a few days later caused no symptoms. Nevertheless subtotal thyroidectomy was advised.

Eruptions thus afforded occasion for discontinuing treatment in four cases. In two of these (*Ho* and *Ku*) the causative rôle of thiouracil appeared to be approximately established.

*Fever*. An elevated temperature of undetermined origin occurred in *Mc* and *Sh*, patients who as already mentioned died of circulatory failure. Fever

was also encountered as an accompaniment of eruption in Ho. It was the cause of discontinuance of treatment in the following case.

*Li*, a woman of 50, had an unexplained fever ranging between 36.6° and 38° C. during a control period preceding therapy. During the first 10 days of the thiouracil treatment fever of similar degree continued. On the eleventh day it reached a level of 38.8° and on the fourteenth when the drug was discontinued the afternoon temperature was 39.8°. Thirty hours later the temperature was normal. For the next three days it ranged between 37° and 37.8°. A test dose of 0.2 gm. of thiouracil was then given and was followed by an immediate rise in temperature which subsided in 24 hours, and remained normal for 10 days when a test dose of 0.1 gm. was followed by a fever of 38.4°. During these exacerbations the white blood cell and differential count did not change significantly and at no time did they indicate the presence of infection.

It was of special interest that the basal metabolic rates which during thiouracil treatment had been elevated above the level during the control period, fell immediately to normal after the drug had been withdrawn. This suggested the possibility that the drug was successfully affecting thyroxin production even when it was producing toxic reactions in the patients.

#### *Conjunctivitis.*

*Re.* A troublesome conjunctivitis which developed during treatment pursued a variable course with continuance of thiouracil. Evidence that it was independent of the use of the drug came chiefly from the fact that there were several spontaneous remissions during the period when the dosage of the drug was being increased.

*Sl.* A bilateral conjunctivitis of moderate severity twice subsided when the drug was discontinued and twice recurred promptly with its exhibition. It was then decided that the drug should be permanently withdrawn. The spontaneous reappearance of the conjunctivitis after an interval of a week following discontinuance of the drug cast serious doubt on the etiologic relationship.

*Leukopenia and Granulocytopenia.* The fear of agranulocytosis pervaded the entire study. Hundreds of white blood cell counts showing normal values were performed. Considerable variations were encountered and slight temporary leukopenias even to 3,000 were not uncommon. In several instances a fall in the total count was accompanied as in Ch by an increase in the number of immature granulocytes. In most cases, the percentage of granulocytes remained essentially unchanged with minor reductions in total white blood cell count.

In three cases exhibiting leukopenia without granulocytopenia treatment was continued cautiously but intermittently. No correlation of white blood cell count and dosage of drug could be established. The following case is an example.

*Sm*, a woman of 49, had severe thyrotoxicosis complicated by bronchiectasis. During both control and treatment periods she had a moderate fever which seemed to be ascribable to her pulmonary condition. On the fourteenth day treatment was interrupted because of fall of white blood cell count to 2,700 with 65 per cent mature and 10 per cent immature granulocytes. The count returned rapidly to normal and remained at normal levels following resumption of thiouracil six days later.

On three occasions leukopenia without granulocytopenia was the reason for abandoning treatment.

*Ol*, a woman of 50, was treated on the surgical service and was given iodine for 40 days without evidence of benefit. She was then given a test dose of thiouracil. Before the test the white blood cell count was 4,300 with 60 per cent of granulocytes. Immediately following thiouracil the total count was the same but the granulocytes were recorded as 32 per cent. The drug was discontinued. During a period of 25 days in which no treatment was given the white blood cell count varied between 3,300 and 6,000 and the granulocyte count between 26 and 60 per cent. Thiouracil was then given for 12 days in daily doses of 0.8 gm. with variations in white blood cell count from 4,700 to 5,500 and in granulocytes from 54 to 60 per cent. Subtotal thyroidectomy was performed without event at the end of this period.

*Rn* was treated on the surgical service. On the twelfth day of thiouracil a fall in the white blood cell count to 4,000 with 62 per cent of granulocytes was considered sufficient reason for withdrawal of drug and substitution of Lugol's solution. No tests were made to determine sensitivity.

*Wyn*, a woman of 26, had received 35 days of thiouracil treatment with satisfactory control but without complete remission. Her white blood cell count which had been variable then fell to 4,400 with 20 per cent mature and 14 per cent immature granulocytes. The drug was discontinued without further testing and she was transferred to the surgical service.

The following two cases present in bold relief the hazards of thiouracil therapy. The first is particularly terrifying because agranulocytosis developed under close observation in a hospital ward; the second because serious granulocytopenia preceded the appearance of any recognizable symptoms.

*Reb*, a woman of 57, had had two previous subtotal thyroidectomies with later recurrence of thyrotoxicosis. In the summer of 1944 she was treated with thiouracil in the Metabolism Ward. The record of her white blood cell count may be seen in figure 3. During the first 10 days of therapy her white blood cell count varied between 5,400 and 7,000 with no granulocytopenia. On the eleventh day following a short period of nausea and slight fever it fell to 2,300 without significant change in the total granulocyte count. As in several other cases during periods of leukopenia the relative number of immature granulocytes increased in this instance from 4 per cent before to 24 per cent after the development of leukopenia. The drug was discontinued for a period of nine days. Test doses were administered without the development of alarming symptoms. For 25 days thereafter she received daily doses of 0.6 gm. of thiouracil without the appearance of disturbing symptoms. Remission, however, was delayed and it was decided to withdraw thiouracil. She refused to submit to another operation and she was discharged from the hospital on a sufficient dose of iodine. On this regime she gradually lost weight and gradually became more nervous until in February 1945 she was again severely thyrotoxic. Again she refused thyroidectomy. She was therefore readmitted to the hospital where she was given under careful supervision 0.2 gm. thiouracil each day. Again the white blood cell count varied (see figure 3) from 2,600 to 5,400 with granulocyte counts from 50 to 56 per cent. On the twenty-first day of treatment the white blood cell count fell to 2,000 cells with only 2 per cent granulocytes. Thiouracil was discontinued and the following day the white blood cell count was 700 with 1 per cent granulocytes. The pharynx became fiery red; the right tonsil protruded; the temperature rose to 40.1° C.; prostration was extreme. Treatment consisted of penicillin in doses of 25,000 units

every two hours with a great number of remedies aimed at stimulating regeneration of white blood cells. Included were daily intravenous injections of 100 c.c. of crude liver extract in 1,000 c.c. of normal saline and daily doses of 1.0 c.c. of folic acid, 0.2 gm. of pyridoxin and three capsules of yellow bone marrow concentrate. She also received several transfusions and two doses each of 10 c.c. of pentnucleotide. Within 24 hours of the beginning of this treatment the clinical picture was remarkably changed. The pharynx became less inflamed. The right tonsil receded. Prostration was less profound. The temperature fell to 38° C. She remained in this state for seven days without any evidence of improvement in her agranulocytosis. On the seventh day sternal puncture showed 4,200 white blood cells. Most of these were premyelocytes. There were many myeloblasts and megakaryocytes. Several lymphoblasts and normoblasts were seen but only one polymorphonuclear cell could be found.

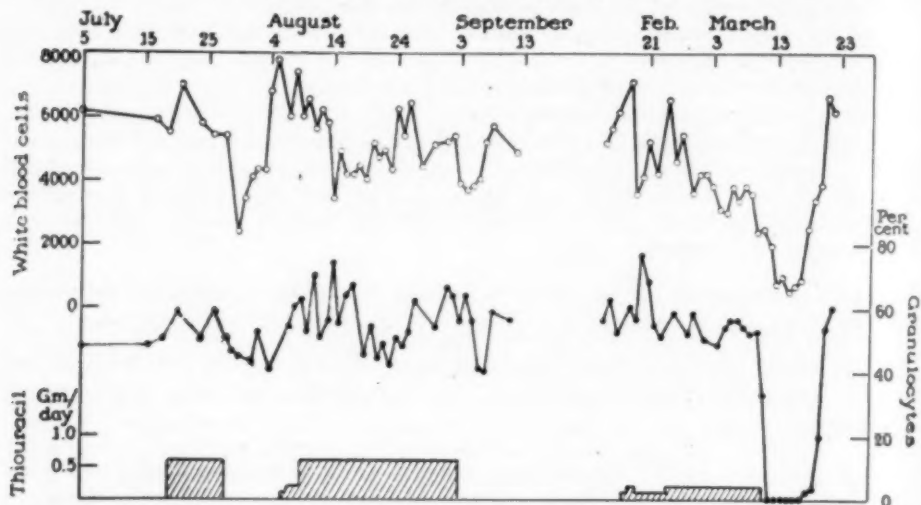


FIG. 3. Record of changes in white blood cells and granulocyte count during thiouracil treatment in Reb.

The following day granulocytes began to appear again in the peripheral blood and she made a rapid and complete recovery. She was later subjected to subtotal thyroidectomy without untoward incident.

It was believed that her life had been saved by the protection which penicillin afforded against the development of serious infection. One could not be encouraged to think that the other remedies had had significant effect upon the rate of regeneration of the bone marrow.

*Pe*, a boy of 16, was treated with thiouracil in the autumn of 1944. Therapy was strikingly successful and he was discharged on maintenance dosage. Because of misunderstanding he discontinued the use of the drug after one month and absented himself from the clinic. In April 1945 he reappeared with relapse. He was started on 0.2 gm. of thiouracil per day without readmission to the hospital. Two weeks later his hyperthyroidism was under partial control; he showed no clinical signs of toxicity but his white blood cell count was found to be only 3,000. He left the clinic before a differential count could be done and could not be located until two days later when his count was 4,900 but with 2 metamyelocytes, 5 band cells and only one mature granulocyte. He still showed no symptoms or clinical signs of toxicity. Thiouracil was withdrawn and the following day he developed sore mouth and a pustule on his ankle. He was given penicillin. His white blood cell count returned to normal in 4 days. The mouth lesions and skin infection healed promptly.

### *Thrombocytopenia.*

*Mis*, a woman of 40, was treated with daily doses of 0.6 gm. of thiouracil for 12 days. It was then noted that the platelet count was low—32,000—and that application of the tourniquet caused appearance of moderately extensive purpura in the skin peripheral to the constriction (positive Rumpel-Leeds test).

Bleeding time was normal but clotting time was prolonged 20 minutes and 30 seconds by the Lee and White method. Three check platelet counts and inspection of the smear confirmed the original observation. There was no evidence of abnormality in red blood cells or white blood cells. Drug was withdrawn. Platelets promptly (48 hours) rose to 240,000. Thiouracil was again exhibited after 10 days and was continued without incident in doses of 0.1 gm. four times daily until basal metabolic rate became normal. Platelet count remained normal. Rumpel-Leeds test was variable but for the most part normal.

### *Nausea and Vomiting.*

*Wal*, a high strung, apprehensive young woman, developed, after four days of treatment, nausea and vomiting which were the occasion of withholding the drug for five days. Renewal of medication in 0.8 gm. and later 1.0 and 1.2 gm. caused no gastrointestinal symptoms.

### *Jaundice.*

*Ro*, a woman of 52, was treated early in the series. The drug was given in amounts varying from 0.6 to 0.8 gm. daily for a period of 21 days. She then noted some anorexia and nausea. The following day she was obviously jaundiced. Thiouracil was discontinued. Icterus index rose to 23, but in 10 days the jaundice had disappeared. Iodine was started at the time thiouracil was stopped. No effort was made in subsequent course to give thiouracil although there was a partial relapse of thyrotoxicosis after discharge from the hospital. Icterus indices obtained after discharge from the hospital and long after discontinuance of thiouracil were intermittently above normal values.

This incident was responsible for studies of icterus index and prothrombin values on all patients treated thereafter. No significant changes were encountered and doubt persisted whether the jaundice in this case could be justly attributed to thiouracil.

### *Hematuria.*

*Wa*, a hypertensive middle-aged man with electrocardiographic changes suggestive of coronary occlusion, had basal metabolic rates which ranged from +24 to +30 and were little influenced by iodine. Thiouracil was exhibited in daily doses of 0.6 gm. for 5 days. He then developed a frank hematuria. There was no crystalluria and no cause for the bleeding was discovered but because of other features of the case, it was decided to abandon treatment. The patient died two months later in circulatory failure. Autopsy was denied.

*Comment.* In considering these 26 untoward incidents, it is impossible to establish definitely the etiological relationship of the drug. In our own estimation a total of five including the two previously mentioned eruptions (*Ho* and *Ku*), one febrile reaction (*Li*), and two granulocytopenias (*Re* and *Pe*) were regarded as probably or certainly ascribable to the drug.

## RESULTS OF MAINTENANCE THERAPY

*Production of Myxedema.* A recognizable hypothyroidism developed in five patients during maintenance therapy. The more significant data concerning them may be seen in table 3. In three of the five cases thyrotoxicosis preceding treatment had been of severe grade. In the other two cases the initial basal metabolic rates were respectively +20 and +25. In one case the first symptoms became apparent within three weeks of completion

TABLE III

| Patient | Sex | Age | Initial B.M.R. | Time of Onset from Start of Treatment (Months) | Time of Recovery following Cessation of Treatment (Months) | Subsequent Course |
|---------|-----|-----|----------------|--|--|-------------------|
| Bi      | F   | 45  | +72            | 2  | 1  | Relapse operation |
| Ga      | F   | 46  | +54            | 4½   | Now recovering   | «                 |
| Be      | F   | 32  | +72            | 6½   | 1  | Relapse           |
| Ze      | F   | 32  | +20            | 4  | 1  | No relapse        |
| Ne      | M   | 58  | +25            | 2  | 6  | No relapse        |

of the intensive therapy. In a second they were evident in the second month of treatment. Maintenance had been continued for 2 to 6½ months in the other patients before symptoms of hypothyroidism were noted. Notes on three of the cases are illustrative of the mode of onset as well as the development and persistence of myxedema.

*Bi* was a woman of 45 with severe thyrotoxicosis complicated by bronchiectasis. Intensive treatment with thiouracil accomplished an excellent result. At the time of her discharge from the hospital her basal metabolic rate was normal but she was complaining of puffiness about the eyes and of a stiffness and full feeling in the arms and hands. A month later, on a maintenance daily dosage of 0.1 gm. she had become obviously and uncomfortably myxedematous with characteristic appearance, dry skin, cold extremities, harsh voice, and impaired hearing. It is notable that while the cholesterol level in her serum had risen to 433 per cent her basal metabolic rate was still within the upper range of normal, +14. The drug was immediately withdrawn. A few weeks later she developed pneumonitis about her bronchiectatic cavities. The thyrotoxicosis recurred. She was discouraged about resumption of thiouracil therapy and was subjected to a successful and uneventful subtotal thyroidectomy.

*Be* was a woman of 32 with recurrent severe thyrotoxicosis. Intensive therapy with thiouracil was most successful and she was easily maintained in a normal state on 0.2 gm. thiouracil daily. In the fourth month of her treatment she took a trip to Cuba. When she returned six weeks later she was complaining of stiffness in arms and hands, and of some puffiness about the eyes. Three weeks later her appearance was characteristically myxedematous. Her skin was dry, her hair was falling, her voice was hoarse and her speech was slow and indistinct. Cholesterol had risen to a level of 468 mg. per cent. Upon discontinuance of the drug, her basal metabolic rate returned rapidly to normal, and symptoms of myxedema disappeared. Within two months thyrotoxicosis was again apparent but was easily controlled by resumption of thiouracil.

Ne was a man of 58 with moderate thyrotoxicosis and a basal metabolic rate of only +25. He was treated with 0.6 to 0.4 gm. of thiouracil daily for 31 days. Intensive therapy was discontinued when the basal metabolic rate reached normal. On a maintenance dose of 0.2 gm. daily the rate continued to fall to -18. Classical signs of myxedema were apparent by the sixtieth day of treatment when the cholesterol had risen to 372 mg. per cent. The drug was then discontinued but signs and symptoms of hypothyroidism persisted. For a time it was thought that the drug might have permanently prevented the formation or mobilization of thyroxin. After six months, however, the symptoms of myxedema gradually disappeared and the patient attained and maintained what appeared to be normal thyroid function. It was of interest that again the level of cholesterol followed more closely the clinical symptoms than did the metabolic rate and that the cholesterol values attained normal levels before the basal metabolic rates.

Certain aspects of these cases were of special interest. It was apparent that the onset of hypothyroidism was not dependent upon the initial degree of thyrotoxicosis. The basal metabolic rates before treatment ranged in different patients between +20 and +72. The development of myxedema did not indicate immunity to later relapse and it is notable that after withdrawal of the drug three of the six cases passed by imperceptible stages from clinically complete myxedema through the normal range to moderately severe hyperthyroidism. Determinations of cholesterol in the serum were found to be of great value in predicting both the onset and the offset of myxedema. In several instances they were shown to parallel the clinical picture more closely than did the basal metabolic rates. The speed with which the edema and major clinical symptoms of hypothyroidism could develop was a matter of considerable surprise. On two occasions patients who presented only doubtful or equivocal signs of diminished thyroid function became dramatically myxedematous within an interval of three weeks.

TABLE IV  
Thyroidectomy Following Thiouracil Treatment

| Patient | Duration of Thiouracil Treatment | Reason for Discontinuing Thiouracil       | Operative Procedure | Outcome of Operation |
|---------|----------------------------------|---|---------------------|----------------------|
| Bi      | 2                                | Relapse following myxedema                | Uneventful          | Satisfactory         |
| Pe      | 2                                | Toxicity                                  | Uneventful          | Satisfactory         |
| Pr      | 6½                               | Projected travel without adequate control | Hemithyroidectomy   | Satisfactory         |
| Ku      | 10                               | Toxicity                                  | Uneventful          | Parathyroid tetany   |
| S       | 7                                | Toxicity                                  | Uneventful          | Satisfactory         |
| Be      | 6½                               | Projected travel                          | Uneventful          | Satisfactory         |

*Thyroidectomies.* In the entire series there were 14 thyroidectomies. Of these eight were performed either because of failure of the drug to benefit (Bn and Bu) or because of toxic reactions during intensive therapy. The other operations were performed for a variety of reasons during the period of maintenance. In table 4, the causes of interruption are listed. It will be

noted that in three instances (Pe, Ku and Sl) the operation became necessary because of toxic reactions whereas in the others it was chosen either because of relapse (Bi) or because of projected travel which would prevent the patient from receiving adequate medical supervision.

All patients were given iodine for a period of at least 10 days before operation. No unusual surgical difficulties were encountered although several glands were vascular and relatively friable. The postoperative course was uneventful and no patient presented evidence of thyroid storm. One patient who had had three previous thyroidectomies developed parathyroid tetany several weeks after the operation.

*Relapse during Treatment.* Two patients relapsed while on maintenance doses and in one of them increase in dosage to 0.6 gm. daily for a period of 37 days was insufficient to restore satisfactory control. The factors determining the relapse were not apparent in either case. Variations in state were encountered in many of the patients and on several occasions it was necessary to vary the dose of thiouracil from 0.1 to 0.2 gm. to maintain an optimum state.

*Withdrawal of Drug during Remission.* In 48 of the 87 patients exhibiting satisfactory remissions the drug has been discontinued. The experience of Astwood<sup>7</sup> led us to expect that remission of symptoms would not be maintained if thiouracil were withdrawn soon after normal conditions were attained. It was planned, therefore, to continue thiouracil for a minimum of six months, from the time of its first exhibition or longer if the control seemed too precarious at the end of that time.

TABLE V

| Patient | Reason for Stopping Treatment | Length of Time Treated, Months | Initial Basal Metabolic Rate | Relapse | Time of Relapse, Months |
|---------|-------------------------------|--------------------------------|------------------------------|---------|-------------------------|
| Ne      | Myxedema                      | 2                              | +25                          | No      | —                       |
| Bi      | Myxedema                      | 2                              | +72                          | Yes     | Immediate               |
| Ze      | Myxedema                      | 4                              | +20                          | No      | —                       |
| Ga      | Myxedema                      | 4½                             | +54                          | —       | —                       |
| Dr      | Not available for treatment   | 3                              | +25                          | No      | —                       |
| Pe      | Not available for treatment   | 2                              | +13                          | Yes     | 3                       |
| Co      | Not available                 | 2                              | +25                          | Yes     | 17                      |
| Le      | Coronary accident             | 2                              | +26                          | No      | —                       |
| She     | Pregnancy                     | 1                              | +23                          | No      | —                       |
| Fr      | Pregnancy                     | 5                              | +40                          | No      | —                       |
| Sm      | Condition justified           | 5½                             | +4                           | Yes     | —                       |
| Fa      | Condition justified           | 5                              | +10                          | No      | —                       |
| Su      | Condition justified           | 3                              | +36                          | No      | —                       |

This intention could not be followed strictly in all cases and there were 13 whose treatment was interrupted for one reason or another before six months had elapsed. These cases are listed with some pertinent data in table 5.

It will be noted that they include four of the five cases which developed myxedema. Another patient (Dr) became too busy with her family to permit sufficient observation so therapy was discontinued without relapse at the end of the third month. Another (Pe) absented himself because of misunderstood directions. Another (Co) quit treatment after three months and was lost to view until 17 months later when she had developed a moderate relapse. It is perhaps significant that this relapse followed a period of considerable distress when her parents took to drink, her child became ill, her sister developed Graves' disease and her husband who had fallen in love with another girl asked for a divorce. The drug was discontinued during a coronary occlusion in Le and was not started again because he never showed any tendency to relapse of thyrotoxicosis. Treatment was withdrawn in patients (Sh and Fr) because of pregnancy. This was done because animal experiments had indicated possible danger of the drug to the development of the fetus,<sup>9</sup> and in spite of clinical experience that thiouracil in pregnancy may not always be demonstrably harmful.<sup>10</sup> In three others (Sin, Ta, Sn) the condition was so satisfactory that a full six months treatment was not considered necessary.

TABLE VI

| Patient | Duration of Treatment, Months | Reason for Withdrawal of Drug | Interval between Withdrawal and Relapse, Months | Apparent Exciting Cause of Relapse | Subsequent Course                 |
|---------|-------------------------------|-------------------------------|---|------------------------------------|-----------------------------------|
| Bi      | 2                             | Myxedema                      | 1   | Bronchiectatic pneumonitis         | Subtotal thyroidectomy            |
| Sm      | 5½                            | Satisfactory state            | 1   | Bronchiectatic pneumonitis         | Controlled by thiouracil          |
| Pe      | 2                             | Unavailable for treatment     | 3   | None discovered                    | Subtotal thyroidectomy            |
| Co      | 2                             | Unavailable for treatment     | 17  | Family difficulties                | Still under trial with thiouracil |
| Ba      | 8                             | Satisfactory state            | 12  | Anxiety state                      | Controlled by thiouracil          |
| Sl      | 7                             | Toxic reaction                | 1   | Anxiety state                      | Subtotal thyroidectomy            |
| Br      | 6½                            | Satisfactory state            | 4   | Psychological trauma               | Subtotal thyroidectomy            |
| McA     | 9                             | Satisfactory state            | 1   | Insecurity                         | Controlled by thiouracil          |
| Ku      | 10                            | Toxic reaction                | 1   | None discovered                    | Subtotal thyroidectomy            |
| Be      | 6½                            | Myxedema                      | 1   | None discovered                    | Controlled by thiouracil          |
| Coh     | 7                             | Satisfactory state            | 2   | Sudden psychic trauma              | Controlled by thiouracil          |

For the whole series the longest time of withdrawal without relapse has been 16.5 months. In another case the interval has been 15 months while in four others it has been more than 10 months. The average time has been 6.1 months and only six cases have been observed for less than two months following the cessation of treatment.

In this entire group of 48 there have been thus far only 11 relapses (22.9 per cent). These are listed with some pertinent data in table 6.

Four of the relapses occurred in patients (Bi, Pe, Co, Sm) who had received the drug for less than six months. One (Pe) had been treated with thiouracil for only two months. Two (Bi and Sm) relapsed during an exacerbation of bronchiectasis. Family difficulties, anxiety states or insecurity may have contributed to several (Co, Ba, Pr, McA, Sl). Relapses occurred in two patients (Kn and Be) who had had previous thyroidectomies and had previously shown marked tendency to recurrence of the thyrotoxic state. The relapse of the last case deserves special mention because of the mechanisms it reveals.

Coh, a hard working florist, emotional, sensitive, and severely thyrotoxic, had been treated by thiouracil with great success. He continued this treatment for seven months. At the end of this time his condition seemed to justify withdrawal of thiouracil. For two months there was no sign of relapse. Then one day, he was coming home from work when he saw a crowd gathered near his house and heard the frantic cries of his young son. Thinking that his boy had met with some frightful accident he ran to where the crowd was gathered, found that his own son was not injured but that a neighbor's boy had suffered a compound fracture from being run over by an automobile. He picked up the boy, carried him home, up two flights of stairs and stood by until the doctor came. That night he could not sleep. The following day he was nervous and distraut. When he presented himself three weeks later he displayed all the evidences of a serious thyrotoxic relapse. Use of thiouracil in doses of 0.2 gm. without interruption of work permitted a satisfactory remission. This was the more remarkable since it took place during the Christmas season when his work as a florist required long hours and arduous labor.

In observing patients following the withdrawal of therapy, it was often difficult to determine whether variations in mood and activity were indicative of relapse. On several occasions there was strong temptation to start the drug again in patients who later had complete remission of all suspicious symptoms. There can be little doubt that in thyrotoxic patients who have undergone remission following the use of thiouracil there is always the tendency to relapse.

TABLE VII

|   |     |
|---|-----|
| Number of Cases Treated.....                                | 100 |
| Unsatisfactory or questionable results.....                 | 27  |
| Failed to respond.....                                      | 2   |
| Died of cardiac complications.....                          | 3   |
| Treatment interrupted because of unfavorable reactions..... | 12  |
| Relapse during therapy.....                                 | 4   |
| Unsatisfactory control during maintenance.....              | 2   |
| Treatment interrupted because of growth of gland.....       | 1   |
| Treatment interrupted by choice of patient.....             | 3   |
| Satisfactory results.....                                   | 73  |
| Satisfactory remission with continuance of therapy.....     | 36  |
| Continued remission after cessation of therapy.....         | 37  |

*Continued Maintenance.* Of the entire group there are 36 patients still under maintenance therapy. Of these there are two whose treatment has been continued for 12 months and 18 months respectively because their re-

mission was precariously and imperfectly controlled. The others have not yet completed six months of therapy.

*Résumé.* In table 7 there is presented a summary of results in the 100 cases. It will be seen that 73 of these are regarded as successful in the sense that remissions have continued during maintenance doses of the drug, or after the drug has been discontinued. Twelve represent flat failures in that the drug either failed to act, relapse occurred during maintenance treatment or patients were not maintained in a satisfactory state. The other cases designated as unsuccessful in table 7 are more difficult to assay in that they represent situations which may or may not have required discontinuance of drug and substitution of other therapy.

#### DISCUSSION

*Efficacy of Thiouracil.* In 73 of the 100 cases the drug has been successful in the sense that it has produced satisfactory remission for periods up to 21 months. It has failed in 14 cases either because it did not control thyrotoxic symptoms or did not maintain the patient in a satisfactory condition. During the course of treatment there were three deaths ostensibly from circulatory complications. None of them could be fairly ascribed to the drug nor did it seem likely that the patients would have been saved by other methods of management. The administration of the drug has been accompanied by 26 unfavorable reactions at least five of which can be attributed to toxic action of thiouracil.

With such a record it is appropriate to ask again whether the drug should be made generally available, whether it can be expected under any circumstances to offer a permanent cure and to what extent it may be used as a substitute for surgical treatment. Some of the data can be used in a partial answer.

*Safety for General Use.* The chief reason now recognized for withholding thiouracil from general use is the danger of agranulocytosis. Experience of reported cases has shown that the occurrence of this serious complication is, within the therapeutic range, not dependent upon the dosage of the drug but is more properly considered as an idiosyncrasy or special sensitization. Circulatory agranulocytosis may precede by several hours the development of any recognizable clinical symptoms and may occur so suddenly that it cannot be forestalled even under the meticulous observation of a well conducted ward. It appears, therefore, that the danger exists even with the most careful management. It is questionable whether the incidence of intoxication is increased by any except the most flagrant abuses. Evidence that this is true is furnished by comparison of Williams' <sup>4</sup> results on ambulant patients with those we have obtained with a group carefully guarded in a hospital ward. It is not apparent that the greater supervision resulted in fewer accidents or more favorable therapeutic results.

One must recognize also that the drug has already been extensively dis-

tributed and has been used under widely variant degrees of scrutiny with a resultant mortality which, though deplorable, may be no higher than that incident to the best of other methods of treatment. Arguments of this kind may justly be advanced in favor of acceptance and a more general distribution of the drug. They must not, however, be used as an excuse for lax supervision of those who receive thiouracil. Consideration of our patient Re demonstrates how urgent and how life saving early recognition and prompt treatment may be after agranulocytosis has developed.

*Permanence of Remission.* Evidence is not yet sufficient to state whether thiouracil can cause permanent remission or cure of thyrotoxicosis. In this series, it is significant that of 47 cases in which the drug was withdrawn for periods from one to 16 and one-half months after two to seven months of treatment there have been only 11 or 23.4 per cent of relapses. All experience with thyrotoxicosis has indicated that those who have once had the disease have a constant or intermittent tendency to relapse. Although this generalization may apply to all thyrotoxic patients, the tendency has been so marked in a few that repeated thyroidectomy has become necessary. Because the tendency to recurrence has been obvious, it is somewhat surprising that so crude a procedure as the removal of an entirely empiric amount of functioning thyroid tissue should so often accomplish satisfactory permanent control.

Since in patients treated with thiouracil no tissue is removed and since production of thyroxin commences soon after the drug is withdrawn one might predict almost immediate relapse when treatment is discontinued. That this does not occur suggests the thesis that effective control of thyrotoxicosis may depend less upon removal of functioning tissue than upon the more or less prolonged interruption of functional disturbances and of vicious cycles of reaction and behavior. That the tendency to relapse persists after thiouracil treatment is attested by the 11 recurrences which we have observed at variable intervals after withdrawal of the drug. In some of the initially more severe cases and particularly in those who had relapsed after previous thyroidectomy recurrence of symptoms started almost as soon as treatment was stopped. In other cases including some of apparent severity, relapse was delayed, in one instance as long as 17 months. Such evidence as has been accumulated in our short series indicates that an important rôle in the timing or in the occurrence of relapse may be played by such factors as insecurity, anxiety states, violent psychic trauma and infection.

*Thiouracil as a Substitute for Surgery.* It does not need to be emphasized that any new remedy for thyrotoxicosis must be good to replace the accepted iodine preparation and operation where operative mortality in the best hands may approximate 1 per cent and where a single thyroidectomy may accomplish control satisfactorily enough to avoid subsequent operations in possibly 85 per cent.<sup>11</sup> Actual relapse rate following surgery is unknown since many patients who have received thyroidectomy are seen only occasionally thereafter. In careful follow-up on small groups many minor and transient relapses are seen.

While it is too early to know whether mortality rate from the accidents of thiouracil is as great as that consequent to the best surgery, it is safe to say that it has been less than the average mortality in thyroid surgery throughout the country. In the 48 patients from whom thiouracil has been withdrawn in this series, 76 per cent have not yet relapsed. It will be seen that this record approximates but does not equal that usually claimed for surgery.

There are a number of relative disadvantages in thiouracil therapy. The period of intensive treatment with the drug is usually more time consuming. In a few cases it approximates the month of treatment which constitutes successful iodine preparation, operation and postoperative convalescence. More often it requires between 30 and 40 days and in a few cases intensive treatment for two or three months may be necessary. This is a matter of considerable consequence if the patient is to be hospitalized during intensive therapy. If as appears possible from Williams' experience<sup>4</sup> thiouracil can be given with relative safety to ambulant patients, the matter is not of so much consequence.

It appears at present, however, that intensive treatment should be followed by several and possibly by four or five months of maintenance therapy during which danger of toxicity still looms as a rare but ominous hazard. Such a course requires much more constant observation and careful scrutiny than does postoperative care. It requires also a high degree of coöperation on the part of the patient, and this is maintained with increasing difficulty as the treatment is prolonged. The complexity of life interposes many circumstances such as employment, family duties and travel which make exact control over long periods difficult or even impossible. Also in young women pregnancy may interrupt the course of treatment before control or optimum effects have been established.

Our own experience as well as that of the literature indicates that large nodular goiters respond less readily to thiouracil and that some of them are extremely resistant to treatment. This fact as well as esthetic considerations and cancer control favor surgery as the treatment of choice in such cases.

On the other hand there would seem to be much evidence that mild and many recurrent cases of thyrotoxicosis are so easily brought under control by thiouracil that use of the drug constitutes the best solution. Furthermore there are not a few cases of Graves' disease that because of circulatory or other complications represent far too great a risk to tempt the most courageous surgeon. For such thiouracil constitutes a boon and a new hope.

#### SUMMARY

1. Report has been made of 100 cases of thyrotoxicosis treated with thiouracil. Remission was induced in 87.
2. The drug exerted a beneficial influence on emaciation, tremor, hyperkinesia and circulatory symptoms; on basal metabolic rate, cholesterol levels and the creatine defect and on the tendency of thyrotoxic patients to lose nitrogen, calcium and phosphorus.

3. Studies of cholesterol levels and the extent of creatine defect were found to be valuable aids in following the effects of the drug.

4. Protrusion of the eyeballs was not lessened but lid spasm and lid lag were improved or controlled.

5. Benefit from thiouracil was often apparent in less than 10 days and normal conditions were usually attained within 40 days. Factors tending to retard the rate of response were previous use of iodine and large nodular goiters.

6. Of the 100 cases, 73 were successful in the sense that they were maintained in remission. In 37 of the 73 the drug was withdrawn for two to 16 and one-half months without relapse.

7. The drug failed to excite favorable response in two, permitted relapse during treatment in four and exerted unsatisfactory control in two.

8. There were three deaths from circulatory complications but none that could be justly ascribed to the action of the drug.

9. In 12 cases, unfavorable symptoms resulted in withdrawal of drug. In five of these there seemed to be little doubt that the untoward symptoms were caused by the drug.

10. Two cases of agranulocytosis were encountered. One was mild and transient; the other was severe and prolonged but recovered after seven days under the protective use of penicillin.

11. Thiouracil is deserving of more extended and more general trial. Evaluation of its rôle as an alternative to surgical treatment awaits further clinical experience.

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## HYPEROPHTHALMOPATHIC GRAVES' DISEASE\*

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My first job obviously must be to define, and defend, the somewhat monstrous title of my paper. The point is that an all inclusive term is needed to cover a spectrum of clinical pictures, probably of the same or similar etiology, which shade one into another. I have used the term Graves' disease for this purpose. Toxic goiter will not do because all the cases in the group are not toxic, nor do they all have goiters. Nor will exophthalmic goiter fill the bill for exophthalmos and related eye signs may be lacking.

Since the etiology of this disturbance is unknown, one is forced to resort to an eponym. Historically Parry is entitled to the honor, but Graves' name is more generally used and is more likely to be understood. It should also be recognized in naming the malady that it is by no means merely a thyroid disease. Rather is it to be looked upon as a widespread imbalance of some sort in which disorder of the thyroid is but one item. Other endocrines than the thyroid are involved, also the muscular, nervous, reticulo-endothelial, and lymphatic systems.

Now what of "hyperophthalmopathic"? The purpose here is to devise a term which will label adequately a subgroup within the general group covered by "Graves' disease," or, in other words, to define a variant from the more usual or classic picture of the malady. The cases in question are, of course, those in which the ophthalmic phenomena overshadow the thyrotoxic, in which, indeed, thyrotoxicosis may actually be absent. My colleagues and I, being dissatisfied with any terms we could find in the literature, have been groping for some years for something better. "Hyperophthalmopathic" is the most recent result of this effort. It is distressingly polysyllabic but seems at least to be clear and accurate. Any case of Graves' disease may be "ophthalmic" or "ophthalmopathic," but the ones in question are unusually badly off as to their eyes—ergo, "hyperophthalmopathic." The term is intended to have no more separative connotation than black measles or galloping consumption. In viewing the whole spectrum of Graves' disease one sees at one end cases with thyrotoxicosis and no eye involvement, and at the other (the hyperophthalmopathic) eye involvement and little or no thyrotoxicosis. In between these extremes there are all sorts of intermediate types. It should be further noted that the type may vary in the individual case. What starts off as classic may later come to fall within the hyperophthalmopathic category. It might be more accurate to say the hyperophthalmopathic *phase* of Graves' disease, rather than hyperophthalmopathic type.

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The hyperophthalmic phase is most frequently seen after thyroidectomy, and one concludes under these circumstances that thyroidectomy had something to do with initiating it, but it also may supervene in the patient without operation.

It also should be stressed that the hyperophthalmopathic phase is relatively more frequent in males than females. To be sure, Graves' disease in toto is far more common in females, but among males with the disease, relatively more are in the hyperophthalmopathic phase than is the case in females.

Surveying then the several phases, or types, of Graves' disease, one may recognize, among others, the following:

Classic Graves' disease—that is to say, with ophthalmopathy, thyrotoxicosis and goiter.

Graves' disease with thyrotoxicosis but no ophthalmopathy.

Hyperophthalmopathic Graves' disease with—

(a) Hyperthyroidism

(b) Euthyroidism

(c) Hypothyroidism.

Particularly interesting are the cases in which there is eye involvement and seemingly nothing else. In making diagnoses in cases falling within the area of Graves' disease, I favor, at present, either preceding that eponym with a suitable adjective as "classic" or "hyperophthalmopathic," or following it with a suitable descriptive phrase, such as "with severe thyrotoxicosis and minimal eye involvement." There may be added also "acute," "chronic," "fulminating," or "recurrent" as indicated. If one grades as to severity either ophthalmopathy or thyrotoxicosis from 0 to +++, then one may say that any of the following combinations may be found in naturally occurring Graves' disease.\*

|   | Ophthalmopathy | Thyrotoxicosis |
|---|----------------|----------------|
| Classic Type or Phase.....                  | +              | +              |
|   | ++             | ++             |
|   | +++            | +++            |
| Graves' Disease without Ophthalmopathy..... | 0              | +              |
|   | 0              | ++             |
|   | 0              | +++            |
| Hyperophthalmopathic, Type or Phase.....    | +++            | 0              |
|   | +++            | +              |
|   | +++            | ++             |

From a classification point of view the eye signs themselves are very numerous. Our major concern is with their significance, and particularly whether there is more than one etiological type of ophthalmopathy in Graves'

\* In this connection it is interesting to go back to 1860 and note that Holthouse, discussing a case of C. H. Jones,<sup>1</sup> remarked that there are three kinds of Graves' disease, one in which the goiter and proptosis appear simultaneously, one in which the goiter preceded the proptosis, and a third in which the proptosis preceded the goiter. He believed the proptosis due to effusion of blood or serum into the orbit.

disease. For practical convenience let us group the ophthalmic phenomena as follows:

(a) *Those related to lid retraction.*

Wide palpebral aperture.

Lid lag.

Staring or frightened expression.

Exophthalmos (some believe the wide separation of lids per se permits protrusion of the globes).

(b) *Those related to extrinsic muscle weakness.*

Limitation of movement of eyeball, especially upward.

Diplopia.

Exophthalmos (in part probably due to weakness of the recti).

(c) *Those due to swelling.*

Exophthalmos (chiefly due to swelling of orbital contents).

Swelling of lids.

Swelling of conjunctivae (chemosis).

As to the pathogenesis and etiology of the ophthalmopathy of Graves' disease there has been speculation for more than two centuries.<sup>2, 3, 4, 5, 6, 7, 8, 9</sup> The evidence available indicates that swelling of the orbital contents is a very important, if not the sole, factor concerned in proptosis of the globes. Weakness of the rectus muscles probably also plays a part, and the wide separation of the lids likewise is believed by some to be a factor.

That lid retraction plays more than an adjuvant rôle seems to me very doubtful. Considerable degrees of lid retraction may occur in Graves' disease without any proptosis.<sup>10</sup> On the mechanism of lid retraction there is lack of agreement. Pochin<sup>11</sup> considers it due to spasm of the levator palpebrae superioris, a striated muscle innervated by the oculomotor nerve, and he believes that sympathetic overactivity has nothing to do with it. Mulvany,<sup>12</sup> on the other hand, believes that lid retraction is due to spasm of Landström's muscle, a smooth muscle innervated by the sympathetic. Landström himself believed this muscle to be the cause of proptosis also, although the muscle lies mainly in front of the globe.

The evidence that swelling of the orbital contents is the major factor in exophthalmos is overwhelming. The questions are, what is the nature of the swelling, and what causes it? Many investigators have considered edema of the entire orbital contents as chiefly responsible.<sup>13, 14, 15, 16</sup> Others have thought that swelling of the extrinsic muscles played the chief part.<sup>17, 18, 19, 20</sup> The recent series of papers by Rundle, Wilson and Pochin<sup>21, 22, 23, 24</sup> from the Westminster Hospital, London, make a strong argument for fat as the important item. These investigators succeeded in obtaining complete dissections of the orbit at autopsy in 17 cases of Graves' disease, and in 12 of them they were able to make exophthalmometric measurements, both ante and post mortem. This is an astounding achievement. It would be difficult in this country these days to gain access to such a mass of material.

The chief point about the Westminster Hospital studies is that they show pretty conclusively that in the cases observed, orbital swelling was largely due to increase in fat. This increase in fat was quantitatively greatest in the orbital fibro-fatty tissue of the orbit, but was relatively greatest in muscles especially the levator palpebrae superioris, which is, they believe, responsible for the lid retraction. Rundle and Wilson<sup>23</sup> further give rather convincing evidence that the bulging of the lids so commonly seen in Graves' disease, and usually attributed to edema, is really due to deposits of fat. They point out that the swelling fails to pit on pressure as edema would, and instead is lumpy like fat. These fat deposits they believe due to a protrusion of fat from the orbit. If the muscles are strong and intraorbital pressure high, fat will ooze out about the eyeballs. Rundle and Wilson minimize the rôle of edema, and perhaps rightly, insofar as the cases they studied are concerned. They furthermore make the following comments: "Hertz, Means and Williams"<sup>25</sup> "have developed the thesis that there are two different types of Graves' disease, the classical form and an 'ophthalmopathic form.' In the former there is exophthalmos and lid lag, in the latter, ophthalmoplegia and severe edema of the orbital and other tissues. But their theory is largely based on a false premise, namely, that edema of the orbital tissues is the proximate cause of the exophthalmos." The last statement of Rundle and Wilson is unjustified. Their series of cases, as far as one can judge from the rather scanty clinical data given, included none of what might properly be called malignant or progressive, exophthalmos, the type in which edema, at least of some of the structures concerned, is unmistakable. The conjunctivae in such cases are often edematous, and various surgeons doing decompression operations on the orbits, have reported edema of the orbital tissue. In the more malignant phases of the process swelling of the extrinsic muscles seems to be the chief factor involved in increasing the volume of orbital contents. Under these circumstances the increased bulk of the muscles appears to be chiefly due to increased water content and lymphocytic infiltration.<sup>16, 26</sup> Furthermore, regarding the question of accumulation of fat in the orbit versus that of water, it should be noted that a number of observers have mentioned the finding of edematous fat.<sup>13, 20</sup>

The precise cause of the swelling in the ophthalmopathy of Graves' disease has not been established with any degree of certainty. It is abundantly evident, however, that the anterior pituitary has something to do with it.<sup>8, 12</sup> Impressive exophthalmos has been produced in a wide range of vertebrate species by administration of anterior pituitary extracts, both in animals with thyroids intact, and in those which have been totally thyroidectomized.

Much point has been made in the literature of the great differences in the anatomy of the orbits in different species, and of the apparent differences in the mechanism of the exophthalmos. It is quite true that these differences exist. For example, Albert,<sup>27</sup> producing a very acute and marked type of exophthalmos by injections of anterior-pituitary extracts in the small fish fundulus, finds that the proptosis is caused by an effusion of fluid into

the orbit. Upon withdrawal of this fluid the exophthalmos disappears. Dobyns,<sup>28</sup> producing exophthalmos in guinea pigs, finds within a few hours of the administration of thyrotropic hormone, deposits of fat along the striations of the extrinsic muscle fibers of the orbit. Later there is Zenker's degeneration of muscle fibers and edematous swelling of the muscle.

In view of these differences it has been argued that the exophthalmos of animals has little or no bearing upon that found in human beings with Graves' disease. But, contrariwise, it has also been assumed that because exophthalmos has been produced by anterior pituitary extracts in animals, the exophthalmos of Graves' disease is due to an excess of thyrotropin. Neither of these conclusions is completely justified. To my way of thinking it is very impressive that pituitary extracts produce exophthalmos in so divergent species as those of fish,<sup>27</sup> ducks<sup>29</sup> and guinea pigs.<sup>30, 31, 32, 33, 34</sup> It is also impressive that many bits of evidence favor the view that there is hyperfunction of the anterior lobe in a human disease of which exophthalmos is a frequent manifestation. But whether the anterior pituitary agent involved is identical with that which exercises the tropic action on the thyroid parenchyma, or something else which comes down in the same fraction, has not yet been determined.

The muscular involvement in Graves' disease is very impressive. It may involve the entire voluntary musculature, but usually produces its most conspicuous result in the eye muscles, because, as Pochin put it, during a recent visit to our clinic, "the orbit is the best tambour in the body." It would seem to be significant that the injections of pituitary extracts in animals produce changes both in the eye muscles and other skeletal muscles, that closely resemble those found in corresponding muscles in Graves' disease of man.

The consequences of the ophthalmopathy of Graves' disease, when it enters what I have called the hyperophthalmopathic phase, exposure keratitis, corneal ulceration and scarring, ophthalmitis with perhaps the loss of one or both eyes, are sufficiently serious to make the solving of the problem of its pathogenesis one of great importance and urgency. The lines of investigation which seem promising, some of which we are following, are first to identify the pituitary factor involved. Is it thyrotropin or something related to it? Next to explore the mode of action of this agent on the tissues of the orbit, and factors which condition or inhibit its action. There is considerable evidence that the action of thyroid hormone antagonizes that of thyrotropin, and there is also the possibility that other substances exist which are antihormonic with respect to thyrotropin. The presence of an excess of fat in the orbit indicates, of course, a thorough study of the entire metabolism of fat in Graves' disease and experimental exophthalmos in animals. The ideal relief or cure of the condition will emerge from an understanding of the fundamental pathogenesis involved, and will supplant the type of therapy, largely symptomatic, which we are obliged to use at present.

The remainder of my time I will devote to the practical problems of diagnosis and treatment.

*In diagnosis* it is a question of recognizing the hyperophthalmopathic phase from the more classic phase. This, as I have tried to indicate earlier, is a matter of relative, not absolute, separation. The arguments of those who, like Mulvany,<sup>12</sup> believe that in hyperthyroidism there are two distinct types of exophthalmos, one of pituitary origin, one of some other origin, leave me unconvinced. Mulvany separates "thyrotoxic exophthalmos" from "thyrotrophic exophthalmos." These would correspond roughly to what I have called respectively the classic and hyperophthalmopathic types of Graves' disease. But whereas Mulvany considers these etiologically distinct, I incline to the view that they are not, agreeing in that respect rather with Rundle and Wilson.<sup>21</sup> The chief reason for my so believing is that all gradations of clinical picture between the extremes can be found, and that often in the same patient one will find at one time the classic picture, at another the hyperophthalmopathic. Mulvany's theories also are at variance with Rundle and Pochin's<sup>23</sup> facts. Mulvany, for example, states that there is no increase in bulk of orbital tissue in the "thyrotoxic" type of exophthalmos, which instead he believes due chiefly to weakness of ocular muscles, whereas in "thyrotrophic exophthalmos" increased bulk of orbital contents, due largely to swelling of the muscles, is the main factor. But Rundle and Pochin proved that there is increased volume of orbital contents in cases which seem clearly to belong to Mulvany's thyrotoxic type. It seems to me easy to believe that muscles which are swollen are also weak, and that most likely they were weak first, and later weak and swollen. What is really needed to settle these points is a method for measuring intraorbital pressure. At the present time Dr. David G. Cogan and I are making preliminary experiments with such an instrument. An efficient method for determining the titer of thyrotropin in the blood would also be of great value.

From the point of view of diagnosis then, as far as I am concerned, at the present time the problem is not one of distinguishing between etiologically distinct types but of deciding in any given case of Graves' disease whether the ophthalmopathy or the thyrotoxicosis constitutes the greater menace to the patient. How to recognize the cases in which the eyes are, or are likely later to make particular trouble, is what needs to be determined. As to the first, there is no real difficulty. That the eyes present a disquieting picture and that the thyrotoxicosis is slight or absent, is obvious. The manifestations which render the eye condition disquieting are chiefly those reflecting swelling and muscle involvement, namely, bulging of the lids, chemosis of the conjunctiva, limitation of ocular movements, and subjectively diplopia. These signs, in our experience, have more diagnostic significance with respect to the hyperophthalmopathic phase than do mere proptosis or the signs related to lid retraction. We have found, as have Rundle and Wilson,<sup>21</sup> that limitation of upward movement is the most impressive and probably the most significant of the muscle phenomena. It is

worthwhile to measure the eye movements in all directions from the straight forward axis. Rundle and Wilson<sup>35</sup> have devised an instrument for this purpose called the vertometer. We have found, however, that the ordinary ophthalmologic perimeter serves very well. With the patient's head stationary, he can be asked to follow with his eyes a flash light which is moved along the arc of the perimeter. When the corneal light reflex leaves the center of the pupil, the limit of movement has been reached, and the angle can be read off in degrees.

The measurement of intraorbital pressure will also be important when it can be quantitated. At present it can be only roughly approximated by palpation. One can get an impression of resiliency in the normal eye, or of doughy resistance in the hyperophthalmopathic eye of Graves' disease by pushing the eyeball back manually with the lids closed.

A much more difficult diagnostic problem is that of recognizing in advance cases in which the eyes are likely later on to enter the hyperophthalmopathic phase—this with a view to prophylaxis. Often of course it is impossible, but one or two suggestive points can be mentioned. For one thing, if the patient is a male, it should be recalled that he has a greater chance of going into the hyperophthalmopathic phase than would a female. The early occurrence of subjective ophthalmic symptoms should also suggest the possibility of an impending hyperophthalmopathic course. We have found, for example, that patients who show this type often consult the ophthalmologist first, because their eyes constitute their sole complaint, whereas those destined to run a classic course are apt to go directly to the physician for symptoms which can be attributed to thyrotoxicosis, and complain but little of eye symptoms. The early occurrence of chemosis and injection of the conjunctivae, and of epiphora are suggestive of the hyperophthalmopathic type, whereas marked lid retraction phenomena with little or none of the phenomena due primarily to swelling, favor the classic type.

*The treatment* of the hyperophthalmopathic type may be divided into specific and symptomatic.

Perhaps deserving of greatest emphasis is a specific, yet negative, form of therapy, namely, the avoidance of thyroidectomy in cases in which the development of a hyperophthalmopathic course is considered likely.<sup>36</sup> Certainly enough cases follow this course postoperatively to justify the belief that the removal of the thyroid played an important part in initiating it.

Patients in whom thyrotoxicosis is slight do not need thyroidectomy for their thyrotoxicosis, and it may aggravate their eye involvement. Under positive measures, more or less specific, we may mention the administration of thyroid, irradiation of the pituitary, and administration of substances antagonistic to thyrotropin.

The administration of thyroid is based, of course, on the theory that excess thyrotropic activity is a major factor, and that thyroid suppresses such action. I have given thyroid to tolerance in a large number of cases, and cannot say that it is productive of very immediate or dramatic improvement.

On the other hand, over a long period of time in many of the cases so treated, the ophthalmopathy at least ceases to progress, and in some there is slow improvement.

Irradiation of the pituitary, in order to reduce its thyrotropic activity, we have tried in only one case. In that one rapid and impressive improvement occurred, but it may not have been due to the treatment. We have not used the method extensively because of fear of impairing other functions of the pituitary. Thompson and Thompson,<sup>37</sup> however, have used it in 38 cases of toxic goiter with fall in metabolism in 23. They do not state what the effects were on the condition of the eyes.

Antithyrotropic substances, for example, the serum of animals immunized against thyrotropin, might neutralize circulating TSH, and if the substance plays a part in the production of the ophthalmopathy, serve to counteract it. Lerman is working on the possibility but has no results to report as yet. The problem is to get a sufficiently pure thyrotropin.

In case of patients in whom ophthalmopathy and thyrotoxicosis are both severe, it is safer from the point of view of the ophthalmopathy to treat the thyrotoxicosis by one of the non-operative methods, e.g., by roentgen-ray or radioactive iodine. These, being slower in action, may be kindlier to the eyes.<sup>38</sup> Drugs like thiouracil, in this regard, are probably to be classed with thyroidectomy. They produce what has been called a medical thyroidectomy, and are to be avoided for the same reasons as surgical thyroidectomy.

Symptomatic treatment of the ophthalmopathy is of several sorts. In the first place, the eyes must be adequately protected. Drying of the cornea with resultant exposure keratitis is the chief danger. Ulceration may follow and perforation. Greasing the eyes at bedtime with plain vaseline, and perhaps keeping the lids closed with tape or bandages may be indicated. Smoked glasses and goggles to keep dust out may also be useful in certain cases.

On the theory that edema of the orbital tissues plays a part, at least in some cases, we have used various depleting measures, for example, diuretics. The results have not been convincing. It is possible that some of the beneficial action of thyroid depends on its diuretic action, rather than on its pituitary inhibitory action. There is one locally depleting procedure which really seems effective. This is one which some of our patients discovered for themselves and told us about, namely, sleeping with the head elevated as much as possible. There seems definitely to be less swelling and feeling of tension in the eyes in the morning in the case of many patients who follow this practice.

Various measures have been aimed at improving the strength or reducing the swelling of the extrinsic muscles. We have, for example, used prostigmine in six cases with no observable benefit. Roentgen-ray treatment to the retrobulbar portion of the orbits has also been tried in a number of cases with questionable benefit in a few. The rationale of this therapy is

that the muscles are the seat of lymphocytic infiltration, which might be dispelled by roentgen-ray with consequent diminution in bulk, and perhaps improvement in muscle tone.

Many surgical procedures from tarsorrhaphy to enucleation have been employed. They are indicated only when the eye is in danger. Tarsorrhaphy for corneal ulceration has sometimes been worth while, but the sutures are very apt to pull out. In marked chemosis, swollen conjunctiva has sometimes been resected. We have had no experience with this procedure in our own clinic.

Decompression by one of several available methods is the most important surgical procedure.<sup>39</sup> It should only be used in progressive exophthalmos when the integrity of the cornea is threatened. When vision is lost and the eyeball is in danger of infection, enucleation is indicated. This is the final operation of defeat.

In conclusion I will suggest that on the theoretical side studies of the action of pituitary extracts on the tissues of the orbit, of the rate of thyrotropin manufacture, of antithyrotropic substances, and of orbital fat metabolism are promising approaches to the underlying pathogenesis of the ophthalmopathy.

On the practical side I would urge that an attempt be made to recognize when patients with Graves' disease are in, or about to enter, the hyperophthalmopathic phase. This is important because the indications for treatment are different from those in the classic case. If recognized prior to thyroidectomy, this procedure should be avoided, and thyrotoxicosis, if it requires any treatment, should be treated by a non-surgical method.

Otherwise the treatment of the ophthalmopathy should be protective and possibly specific by means of thyroid. The surgical procedures should only be resorted to when cornea or eyeball is in danger.

It may be said in closing that in many instances over a period of months, or even years, there is a tendency to slow improvement, or at least cessation of progression, so that one can treat these cases conservatively and expectantly, provided they are kept under sufficient supervision to detect mischief before it becomes irreversible.

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## THE EFFECTS OF THIOURACIL ON THE THYROID GLAND\*

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SINCE Plummer<sup>1</sup> instituted the use of iodine in the preoperative preparation of the thyrotoxic patient in 1923, little has been added to the management of thyroid disease except refinements of technic in the operative procedures. One of the most striking developments in the management of hyperthyroidism has come with the recent advances in chemotherapy. MacKenzie and MacKenzie,<sup>2</sup> in 1943, showed that sulphonamide treated animals developed goiters and hypometabolism. Astwood<sup>3</sup> sought a substance allied chemically to the sulphonamides which would be less toxic to human beings. After experimentation, he chose thiourea and thiouracil as the chemicals of least toxicity. He reported the clinical management of eight cases.

Since his report, thiouracil has been used almost entirely, and numerous articles, both clinical and experimental, have appeared in the literature. In most of these papers, the authors consider thiouracil, administered over a long period of time, as a substitute for surgery in the treatment of hyperthyroidism.

In this study, thiouracil has been used, not as a substitute for operation, but in the preparation of patients for operation as iodine is used and, therefore, the thiouracil has been administered over a relatively short period of time. In one exception, however, the drug was administered for seven months. A few examples, including this exception, have been chosen to illustrate the effects of thiouracil on the histology of the thyroid gland.

### CLINICAL AND HISTOLOGICAL DATA

*Thiouracil Preparation of a Thyrotoxic Patient.* C. G., a colored female, 31 years of age, was admitted to the Elizabeth Steel Magee Hospital on May 19, 1944 with the characteristic findings and symptoms of a diffuse toxic goiter of four months' duration. No iodine had been administered at any time and the basal metabolic rate on admission was +53 per cent. She was placed on thiouracil 0.2 gram, t.i.d., for a total dosage of 6.6 grams. The basal metabolic rate dropped to +16 per cent and subtotal thyroidectomy was performed ten days after starting the drug. There was only a moderate postoperative reaction. Forty-six grams of the gland were removed. It lacked the typical wet, vascular, friable appearance seen grossly in other thiouracil treated glands. Microscopically, this gland (figure 1) is one of the best examples of the changes induced by the drug. The acini are often without lumina and the ones with lumina contain a small amount of stringy, serum-like material. Occasionally, small compact particles of colloid are seen. The cells are tall, averaging 20 micra

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high, with pale cytoplasm. The nuclei are vesicular and are toward the center of the cell, measuring as much as 10 micra in diameter. The picture is that of marked hyperplasia.

*Thiouracil Followed by Iodine Therapy in a Patient Who Developed Toxic Manifestations.* E. M., a white female, 39 years of age, was admitted on June 4, 1944 with a severe, diffuse toxic goiter. Basal metabolic rate on admission was +49 per cent. There was a history of iodine administration one and a half years before admission,

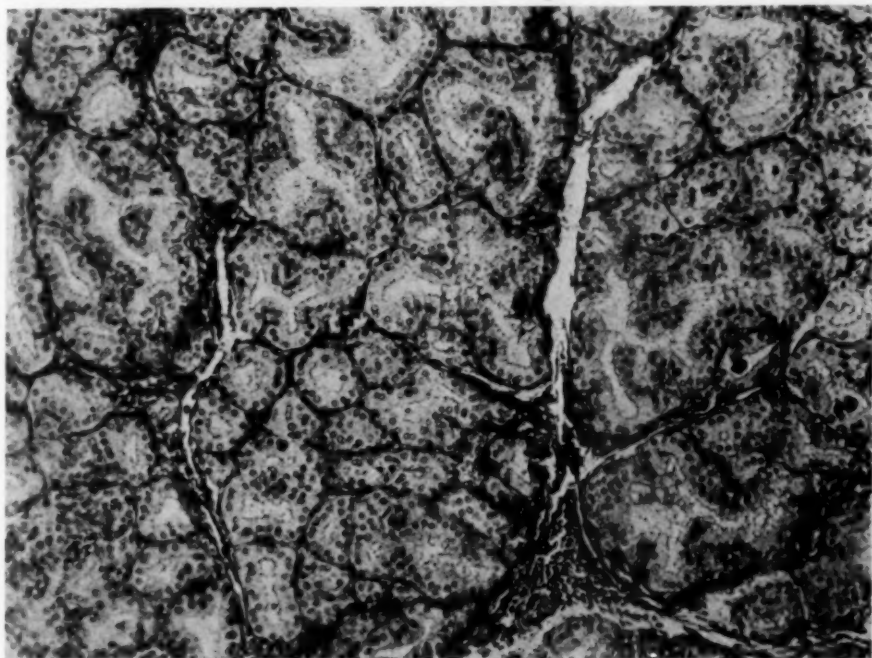


FIG. 1. Thiouracil effect on a toxic goiter. The cells are tall and pale, the nuclei are large and toward the center of the cell. The acini are small and empty. Two small dark staining masses of inspissated colloid are seen.  $\times 135$ .

when the diagnosis was first made. No iodine therapy had been used immediately before admission. Thiouracil, 0.2 gram, t.i.d., was given for nine days for a total of 5.4 grams, when, because of an exacerbation of all the hyperthyroid symptoms associated with a diffuse macular rash, temperature elevation and nausea, the thiouracil was stopped. After a sharp drop in temperature and disappearance of the toxic symptoms, the drug was again started five days later. Almost immediately there was a return of the toxic symptoms, with temperature elevation, marked acceleration of pulse, excitement, nausea and the macular rash. Basal metabolic rate at this time was reported as +70 per cent. The drug was again stopped, and Lugol's solution was started min. XV, t.i.d. Four days later, the basal metabolic rate was +25 per cent. A subtotal thyroidectomy was performed eight days after stopping the thiouracil, and the gland removed was markedly vascular, very friable, and weighed 39 grams. Postoperative course was rather stormy, requiring secondary closing of the wound because of uncontrolled oozing from the cut surface of the gland. Microscopically (figure 2) most of the acini are distended with colloid which is separated from the cells in a droplet-like arrangement of clear spaces. The cells are not so tall as the cells in the thiouracil prepared gland, and the nuclei are at the base of the cells.

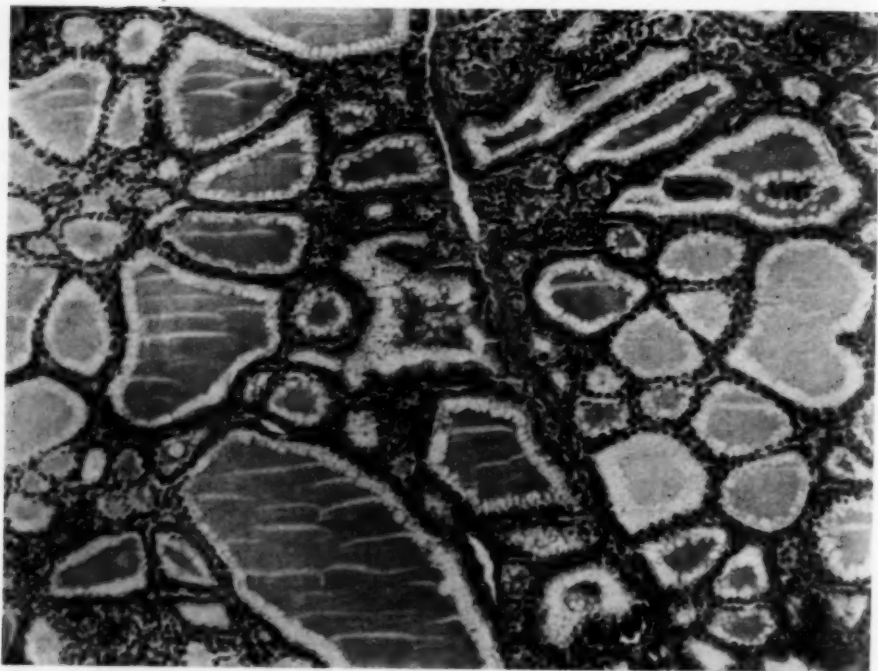


FIG. 2. This illustrates the involution in a toxic goiter after iodine preparation.  $\times 115$ .

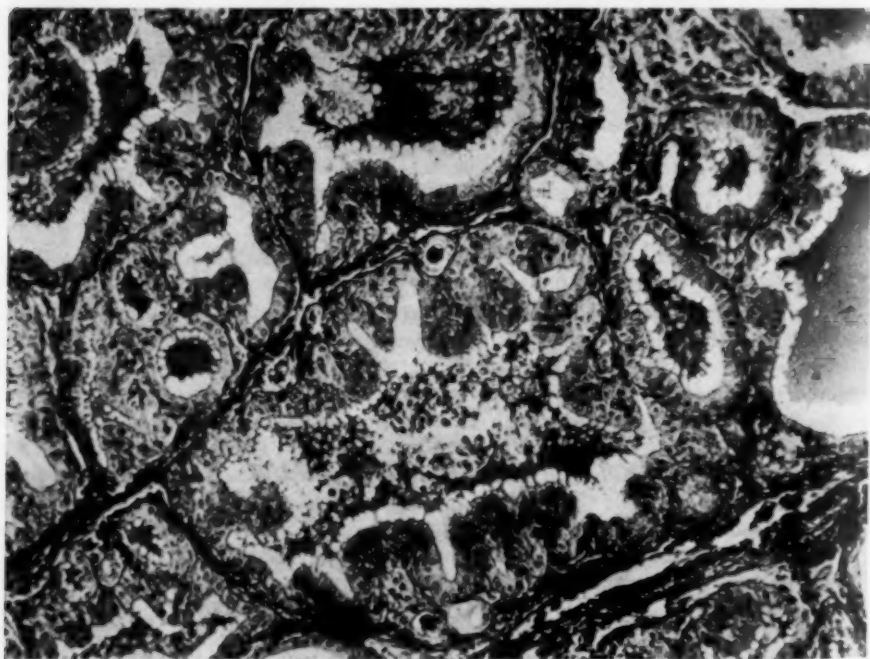


FIG. 3. A very hyperplastic thyroid after iodine preparation.  $\times 135$ .

The microscopic appearance of this gland is typical of the involution changes seen in toxic goiter after iodine therapy.

*Comparison of Iodine Prepared Lobe and Thiouracil Prepared Lobe in the Same Patients.* (1) V. E. Y., a white female, 25 years of age, was admitted on October 27, 1943 because of residual hyperthyroidism complicated by congenital heart disease. She had been operated upon in 1940 for an acute diffuse toxic goiter. Basal metabolic rate on the present admission was +18 per cent. Thiouracil, 0.2 gram, t.i.d., was given for 10 days, then increased to 0.2 gram five times daily. Operation was performed 28 days after thiouracil was started, a total of 24 grams having been given.

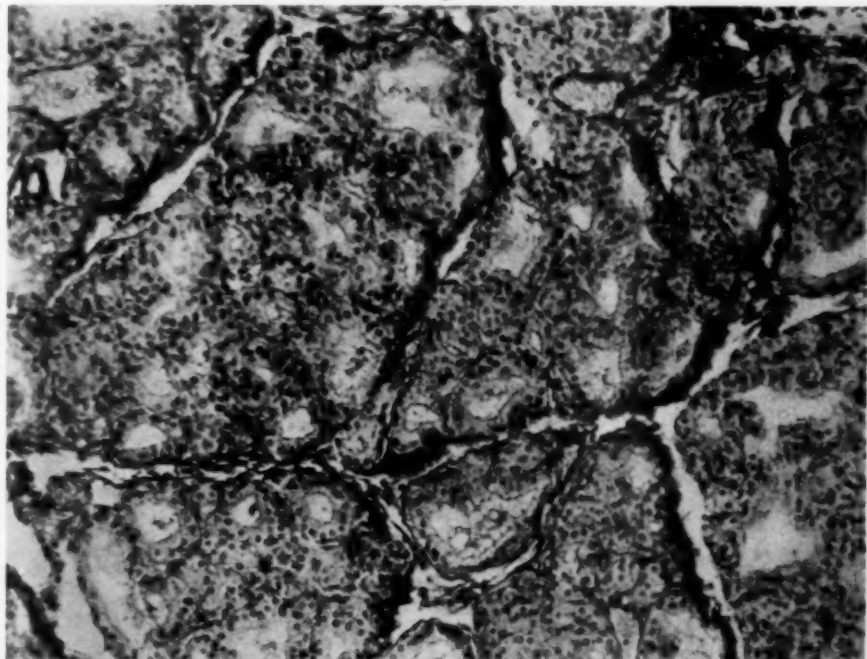


FIG. 4. The appearance of the gland after thiouracil preparation. This lobe is from the same patient illustrated in figure 3, removed three years later because of residual hyperthyroidism.  $\times 135$ .

The thyroid tissue removed weighed 7 grams and was very friable and bled quite freely. Postoperative convalescence was uneventful. Basal metabolic rate on discharge from the hospital was +1 per cent. The gland prepared with iodine and removed in 1940 (figure 3) shows marked hyperplasia with acini containing a stringy, granular colloid. The cells are tall and infolded with small nuclei toward the center of the cell. The portion of gland removed in 1943 following thiouracil preparation (figure 4) resembles the typical thiouracil prepared gland shown in figure 1 so closely that it is almost impossible to distinguish between them. Notice, again, the small acini, absence of colloid, tall cells, pale cytoplasm, nuclei in centers of the cells, and the small tight masses of colloid.

(2) H. D., a white female aged 44, was first admitted on September 10, 1943 with a diagnosis of pericardial effusion and diffuse toxic goiter. Basal metabolic rates ranged from +60 per cent to +40 per cent. Operation was deferred because of the recent pericardial effusion. Patient was readmitted six months later, at which time the basal metabolic rates were +84 per cent and +51 per cent. She was prepared

with Lugol's solution min. XV, t.i.d., and a left lobectomy was performed 28 days later with a moderately severe reaction. Twenty-one grams of gland were removed. The patient was readmitted to the hospital for final lobectomy four months later. The basal metabolic rate was +35 per cent and the patient had regained 20 pounds in weight. She was placed on 0.1 gram of thiouracil, six times daily, for 16 days, receiving a total of 9.6 grams. At the second lobectomy 16 grams were removed. The tissue was pink, watery and friable and there was considerable oozing of blood at operation. Convalescence was complicated by a marked thermal response of 103° to 105° F. in the first three postoperative days. The basal metabolic rate, on discharge, was -4 per cent, 11 days after final lobectomy.

The lobe removed after iodine preparation varied in its histological appearance. The area photographed (figure 5) shows hyperplastic acini distended with colloid.

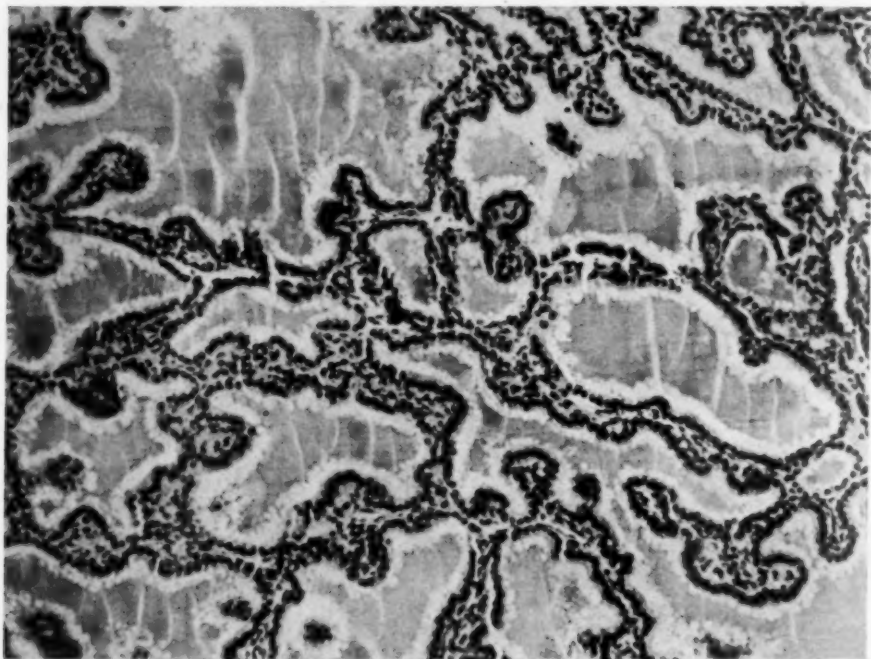


FIG. 5. A small area of toxic goiter after iodine therapy. The infolding and papillary arrangement are suggestive of tumor.  $\times 115$ .

The histology of the lobe removed after thiouracil preparation is even more variable than the iodine prepared lobe. It seems, at first glance, that the thiouracil had no effect on this gland and the appearance is not that of hyperplasia; in fact, the picture (figure 6) is that seen in simple colloid goiter. However, with further search, small patches of hyperplasia were found scattered through the gland and in these patches the characteristics of the thiouracil effect were seen.

*Thiouracil Therapy for Seven Months.* B. M., a white male 67 years of age, was admitted in July 1943 with a diagnosis of diffuse toxic goiter and a left lobectomy was performed following preparation with Lugol's solution. Four months later, November 9, 1943, the patient was admitted again for lobectomy. Thiouracil, 0.2 gram, t.i.d., was started and increased to 0.2 gram five times daily, three days later, and further increased in another three days to 0.2 gram six times daily. A final

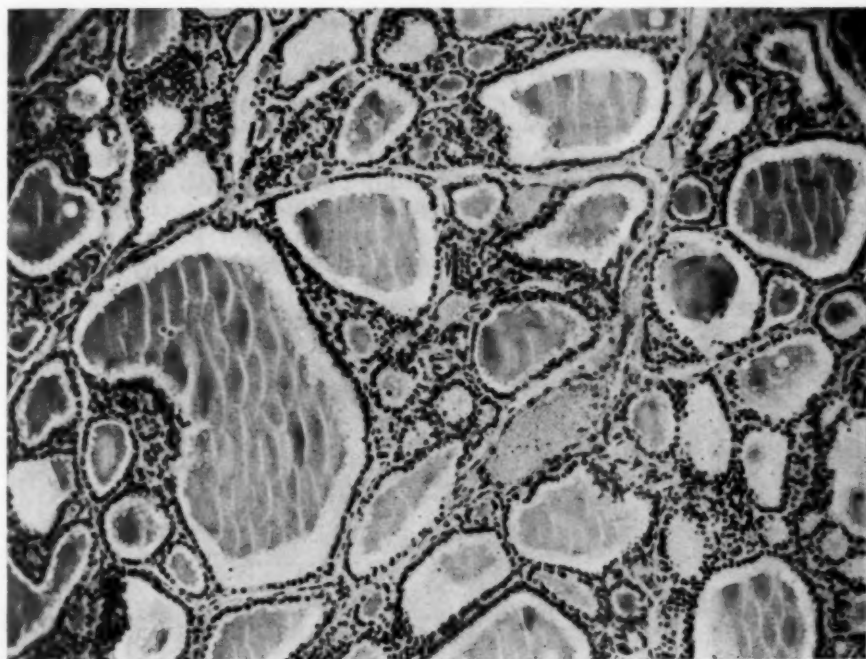


FIG. 6. Simple colloid goiter unaffected by thiouracil.  $\times 115$ .

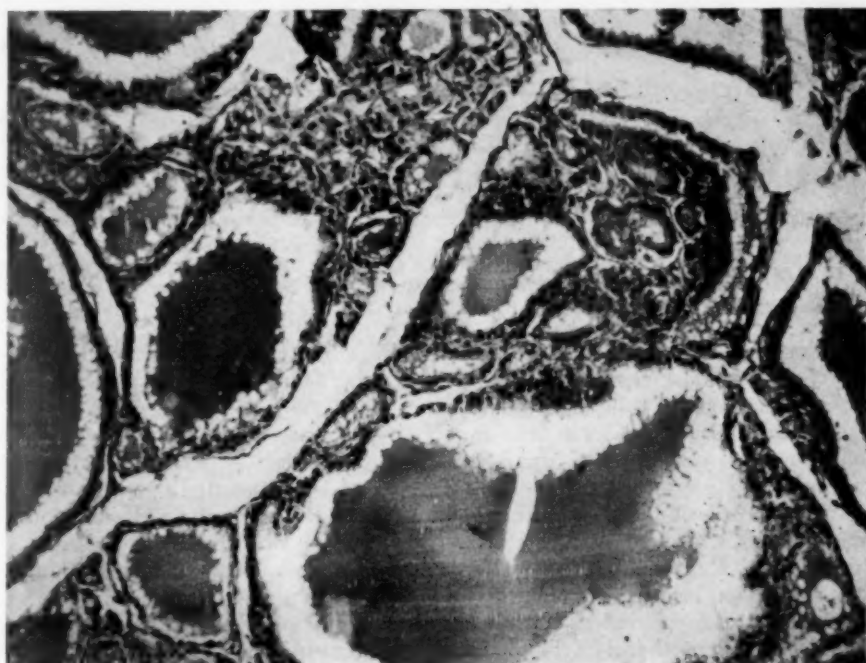


FIG. 7. Patchy architecture in an old toxic goiter after seven months of thiouracil therapy.  $\times 135$ .

lobectomy was attempted one month later after a total dose of 28.8 grams of thiouracil had been given. The patient's condition became alarming after the initial skin incision was made and the operation was stopped. He was discharged from the hospital in four days on 0.2 gram of thiouracil, t.i.d. This medication was continued until readmission to the hospital seven months later because of persistence of his symptoms. Basal metabolic rate, however, was  $-3$  per cent and  $-4$  per cent on consecutive days. Final lobectomy was completed without difficulty three days after admission, and 36 grams of gland were removed. This patient had a total dosage of 135.0 grams of thiouracil over a period of seven months. Basal metabolic rate on discharge was  $+8$  per cent. In this case the microscopic appearance was at variance with the clini-

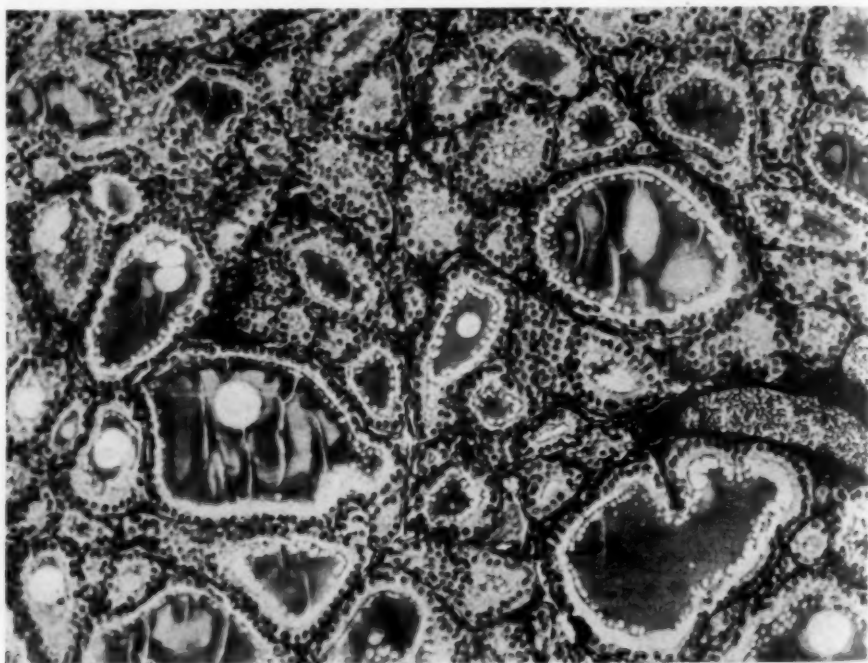


FIG. 8. Toxic goiter resembling involution following iodine. This patient was treated with thiouracil for 19 days before thyroidectomy, but had been on iodine for many months before thiouracil was given.  $\times 135$ .

cal findings and, also, with the microscopic findings in other glands treated with thiouracil. Small and large acini are seen, none of them definitely hyperplastic (figure 7). Most of them contain colloid.

*Thiouracil Treated Gland in a Patient on Prolonged Iodine Therapy.* K. H., a white male 44 years of age, was admitted on November 14, 1943 with a diagnosis of recurrent diffuse toxic goiter. This patient had been operated upon by one of us (J. W. S.) in April 1937 for diffuse toxic goiter. He was quite well following the first operation, except at periods each year when he suffered from ragweed allergy (hay fever). Recurrence of the allergic condition required the administration of Lugol's solution in order to control loss of weight and tachycardia. The period immediately before admission, concurrent with his hay fever, was attended by marked exaggeration of his thyroid symptoms and enlargement of the gland itself. He had been taking iodine up until the time of his admission in the form of Lugol's solution min. V, t.i.d., with no benefit. Thiouracil, 0.2 gram, was administered five times

daily for seven days. The dose was increased to 0.2 gram six times daily for an additional 12 days. The total dose of thiouracil was 21.4 grams over a period of 19 days, after which subtotal thyroidectomy was performed. The basal metabolic rate was +28 per cent. At operation the gland was friable and bled freely, and 36 grams were removed. Postoperative course was stormy with a thermal response to 105.3° F., and secondary closure of the wound was necessary because of excessive oozing from the gland.

The iodine treated portion, removed in 1937, was extremely hyperplastic. The portion removed in 1943 illustrates the lack of thiouracil effect in a gland treated with iodine over a long period (figure 8). In fact, it can serve as a good example of an iodine treated toxic gland, with involution. The cells are moderately tall and most of the acini contain colloid. Comparison with figure 1 reveals the absence here of the hyperplasia seen in the typical thiouracil treated gland.

### DISCUSSION

Thiouracil, when not toxic to the individual, will control clinical hyperthyroidism in the operated as well as in the unoperated patient. In most cases, the thiouracil treated gland offers greater technical difficulties to the surgeon because of the increased vascularity and friability of the gland. In addition, the very toxic patient prepared for operation with thiouracil may have a stormy postoperative course, at times bordering on thyroid crisis.

The individual dosage and the length of time of administration have varied widely in the cases studied. It would appear that if thiouracil is to be used in preparation for operation, standards must be set up to determine when the patient is ready for operation. It is evident that the standards used for iodine prepared patients are not suitable for patients prepared with thiouracil. It is our opinion that iodine still is the drug of choice in the preparation of the thyrotoxic patient for operation.

Histologically, the human thyroid gland removed after preparation with thiouracil is markedly hyperplastic. It resembles closely the glands in experimental animals after administration of sulfaguanidine and thiourea as shown in the illustrations by MacKenzie and MacKenzie.<sup>2</sup> The cells are tall, have pale, finely granular cytoplasm with large nuclei occupying the center of the cells. The acini have small lumina and, at times, papillary infolding is seen. The colloid content is scarce, although some of the acini contain a thin stringy colloid. Occasionally, a small bit of deeply staining material is seen resembling inspissated colloid. Thin walled blood sinuses often traverse the gland. Degeneration sometimes occurs in areas where the cell outlines are distorted and the cytoplasm takes on a deeper stain. Small islands of lymphocytes may be seen. Lymph follicles are seldom seen, although Means<sup>4</sup> and his group show such an example after 17 days of therapy.

Graham<sup>5</sup> pointed out that the thiouracil treated gland resembled the gland in hyperthyroidism before the use of iodine and stated further that the gland in endemic goiter also approximated the appearance of the thiouracil treated gland. Figure 9 is a photomicrograph of an untreated toxic goiter

removed in 1918. The hyperplasia is striking and the lumina contain very little colloid. The cells, however, are not as tall nor are they as granular as the cells in the thiouracil gland. Compare with figures 1 and 4.

The length of time the drug is used seems to affect the histologic appearance of the gland. In this series all but one were treated over a short period of time, 28 days or less, and the description of the thiouracil treated gland is based on the appearance of the gland tissue removed after a rela-

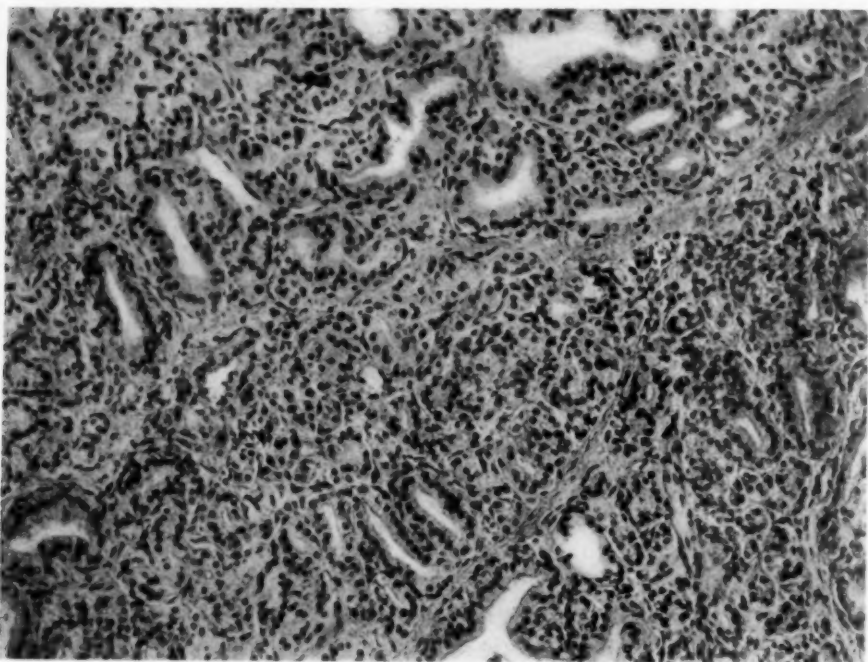


FIG. 9. Diffuse toxic goiter removed in 1918 before the days of iodine therapy.  $\times 135$ .

tively short time treatment. The one exception was a man treated for seven months and the appearance of the gland, figure 7, differs considerably. There are many acini widely distended with colloid, taking on the appearance of the gland undergoing involution. However, there are areas where the acini in small patches fit the description of the thiouracil treated gland.

The patchy distribution of the thiouracil effect may, at first glance, be confusing. In figure 6 there is no evidence of hyperplasia. The photomicrograph might well be that of a simple colloid goiter. Although most of the gland had this appearance, small scattered patches did show hyperplasia. It seems that the drug has little effect on the histology of colloid goiter and acts only on those portions of the gland that are hyperplastic at the beginning.

When iodine is given, following thiouracil, as in the case that developed toxic symptoms, illustrated by figure 2, the appearance approaches that of

the iodine prepared gland. This patient received the drug for nine days followed by a five day rest period and eight days of Lugol's solution before thyroidectomy. It might be said that thiouracil was not given over a long enough period. Astwood<sup>3</sup> observed a latent period of one or two weeks before the effects of the drug were noticed. On the other hand, figure 1 was made from the gland of a patient who was on thiouracil for 10 days only before thyroidectomy and the illustration is one of the best examples of thiouracil effect. Therefore, in this case (figure 2) at least, iodine quickly overcame the changes produced by thiouracil.

Similar masking is shown in the case of the man given thiouracil after prolonged iodine therapy. Even though he was given thiouracil for 19 days, the appearance was still that of the iodine prepared gland (figure 8) and the thiouracil effect was not seen histologically.

It is important in attempting to interpret confusing findings in thyroid pathology to remember that it is not always possible to correlate clinical and pathologic pictures. This fact is ably discussed by Graham<sup>6</sup> and illustrated by a diagram at the end of his article.

#### SUMMARY

The thyroid gland removed after preparation with thiouracil is red, moist and friable and offers greater technical difficulties to the surgeon than the iodine prepared gland. In some individuals, thiouracil is toxic. Some very sick patients may have a stormy postoperative course. Iodine, therefore, seems to be the drug of choice, thus far, in the preparation of thyrotoxic patients for operation.

The histology of the thiouracil treated gland shows marked hyperplasia with tall pale cells and large nuclei toward the center of the cell. Colloid is practically absent. The picture resembles the histology of the toxic goiter before the days of iodine preparation. Iodine administered either before or after thiouracil seems to mask the picture of hyperplasia seen when thiouracil is used alone.

Thiouracil in this study was supplied through the generosity of the Lederle Laboratories, Inc., under the trade name "Deracil."

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## TREATMENT OF POSTPNEUMONIC THORACIC EMPYEMA WITH SULFONAMIDES, PENICILLIN AND REPEATED THORACENTESES \*

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THE principles to be considered in the treatment of pleural empyema are twofold, sterilization of the exudate within the pleural space and obliteration of this space by reëxpansion of the lung. Where this can be accomplished without the development of dense pleural adhesions the early recovery of the patient without any permanent respiratory limitation is enhanced. In most standard treatises on the treatment of postpneumonic empyema thoracostomy, preferably with rib resection, is emphasized. Since Graham and the Empyema Commission<sup>1</sup> in 1918 demonstrated the importance of delaying operation until the pleural exudate had become thickened, open thoracostomy has been highly successful. Some disadvantages to thoracostomy, however, do exist. Osteomyelitis of a rib, delayed or incomplete reëxpansion of the lung necessitating secondary operations either on the rib cage or in the nature of a decortication of the lung, pericarditis, broncho-pleural-cutaneous fistula and metastatic abscess are not infrequent complications and are the cause of a small but definite mortality rate. The principle of allowing the exudate to become thickened succeeded in lowering the high mortality rate attendant in operating upon postpneumonic empyema by awaiting the formation of adhesions. This prevented acute changes of pressure within the thorax which produced such occurrences as mediastinal shift and pulmonary edema. However, in allowing the exudate to become thickened and pleural adhesions to form, the seed was laid for the development of adhesions of the visceral pleura which in some instances precluded a proper reëxpansion of the involved lung. Nevertheless, this principle in the surgical treatment of postpneumonic empyema proved to be sufficiently satisfactory for it to remain as the guiding dictum in the treatment of empyema up to this time.

Continuous closed intercostal suction or tidal drainage has been advocated and successfully used in numbers of instances. This procedure has certain definite disadvantages and there does not seem to be any real agreement on the technic or apparatus that is most effective.<sup>2, 3, 4</sup> Apparently it is most difficult to continue any type of closed intercostal drainage over a period longer than two or three weeks without leakage around the tube, development of secondary infection and pyopneumothorax and in a great many cases treated in this manner secondary rib resection was found to be necessary.

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The use of simple multiple aspirations offered little hope for cure, although it had been used occasionally with success,<sup>5</sup> until the advent of sulfonamides. With the use of these drugs to sterilize the pleural exudate repeated thoracenteses could then be utilized as a hopeful procedure. With the advent of penicillin another powerful antibiotic has been added to our armamentarium. By 1940 several cases treated with sulfonamides and multiple aspirations were reported in the literature, and in 1941 Keefer and his associates<sup>6</sup> in a study of hemolytic streptococcus pneumonia and empyema reported the recovery of four cases of streptococcus empyema by the use of sulfonamides and multiple thoracenteses without operation.

About this time it became evident to many surgeons and it was reported in the literature by Lanman and Heyl<sup>7</sup> and also by Burford and Blades<sup>8</sup> that in cases of pneumonia treated by sulfonamide therapy, in which the sulfonamides had been continued following the development of empyema, the pleural exudate was quite different in character from that seen in postpneumonic empyema observed before sulfonamide therapy came into use. Lanman and Heyl thought that the pus was thickened and more tenacious. Burford and Blades pointed out that the clinical course of the empyema was considerably modified, that the pleural exudate took a longer time to become sufficiently thickened to attempt surgical drainage, and that there was a tendency to multiple loculation within the pleural space. These latter surgeons thought it advisable to discontinue the use of sulfonamides when an empyema developed during the course of a pneumonia. These changes observed in the pleural exudate in empyema caused a certain amount of hesitancy and indecisiveness in the minds of a number of surgeons. Whereas in the past the proper point in the course of the disease to select for surgical intervention had been well recognized, some confusion as to the proper method of handling postpneumonic empyema in sulfonamide treated cases began to develop. Without any specific reference it appeared that some physicians thought that sterilization without complete evacuation of the pleural exudate was sufficient for a cure.

The purpose of this report is to relate the experiences and to draw certain conclusions incurred with the handling of 14 cases of postpneumonic pleural empyema. All cases were treated with sulfonamides and repeated thoracenteses, and in addition three cases received penicillin. During the year 1942 we began to receive in this general hospital a group of cases of postpneumonic empyema treated at various station hospitals in this Service Command. All of these cases had had sulfonamide therapy and one or more thoracenteses before admission here. Owing to the fact that these cases were treated in different hospitals and no standard method of therapy had been initiated, they presented varying clinical pictures. On admission to this hospital seven of these cases presented the picture of an empyema in which the pleural space had been sterilized but considerable exudate remained. In three cases no free exudate was present in the pleural space and only thickened pleura remained. None of these cases was acutely ill and

we determined to try the effect of repeated thoracenteses with the results as outlined in the following case reports. Early in the course of this period of time two cases of acute empyema were admitted from station hospitals, and as our experience at that time was limited they were transferred to the surgical service for treatment. Later four cases of acute thoracic post-pneumonic empyema developed on our own service and were treated with available antibiotic drugs and repeated thoracenteses.

#### CASE REPORTS

*Case 1*, aged 22, developed lobar pneumonia on the left, was admitted to a station hospital April 11, 1942, and was placed on sulfathiazole therapy. On April 24 he developed an empyema on the left, and on April 29 about 300 c.c. of greenish, relatively thin fluid were aspirated. A short chain streptococcus was found on smear but did not grow out on culture. His temperature which had been elevated to about 102° F. fell to below 100° F. following thoracentesis. On May 1, 50 c.c. of exudate were aspirated. He was received at O'Reilly General Hospital May 14, and on May 22, 150 c.c. of thin fluid which was sterile on culture were removed by thoracentesis. By the first week in June he became completely afebrile, began to gain weight, and became ambulatory. By June 25 a roentgenogram showed only slight thickening of the pleura on that side. He was returned to limited duty because of previously existing bronchial asthma on November 23, 1942.

*Case 2*, aged 21, developed a lobar pneumonia on the left and was admitted to a station hospital March 17, 1942 where he was placed on sulfathiazole and later sulfadiazine therapy. About April 26 he developed an empyema on the left and on April 29, 300 c.c. of seropurulent fluid were removed by thoracentesis. Culture showed a nonhemolytic streptococcus. Following this thoracentesis his temperature fell from the level of about 102° F. to below 100° F. until May 7 when it rose to 103° F. He was transferred to O'Reilly General Hospital May 14, and on May 16, 375 c.c. of a yellow, somewhat thick seropurulent sterile fluid were aspirated. On May 19 his chest was again tapped and cloudy sterile fluid which was definitely thinner in character was removed. The temperature then fell to below 100° F., by June 13 the temperature returned to a normal level, and by June 26 he became ambulatory. A final roentgenogram taken September 3 showed only minimal pleural thickening, and he returned to full duty October 26, 1942.

*Case 3*, aged 37, developed scarlet fever March 17, 1942 and was admitted to a station hospital on that date. On March 26 he developed pneumonia in the left side and was placed on sulfathiazole therapy. On April 11 he developed pyrexia for 11 days and continued to run a low-grade fever following that. On June 1 a localized area of empyema was found and on June 9 a thoracentesis produced 150 c.c. of yellow pus which showed pneumococcus and staphylococcus on culture. On June 19 thoracentesis was done, and 150 c.c. of pus were evacuated. He continued to be febrile and on June 25 was received at O'Reilly General Hospital. Repeated thoracenteses were done, which yielded on June 29, 875 c.c. of sterile purulent fluid, July 3, 1,000 c.c. of sterile purulent fluid, July 9, 575 c.c. of sterile thin fluid, July 13, 14 c.c. of slightly thicker fluid and on July 15, 80 c.c. of a moderately thick fluid. Small amounts of saline were used to irrigate the pleural space on June 29 and July 3. By July 17 his temperature fell to below 100° F., became normal on July 27, and remained so. At this time he began to gain weight and shortly thereafter became ambulatory. A roentgenogram taken August 12 showed moderate pleural thickening and he returned to full duty November 6, 1942.

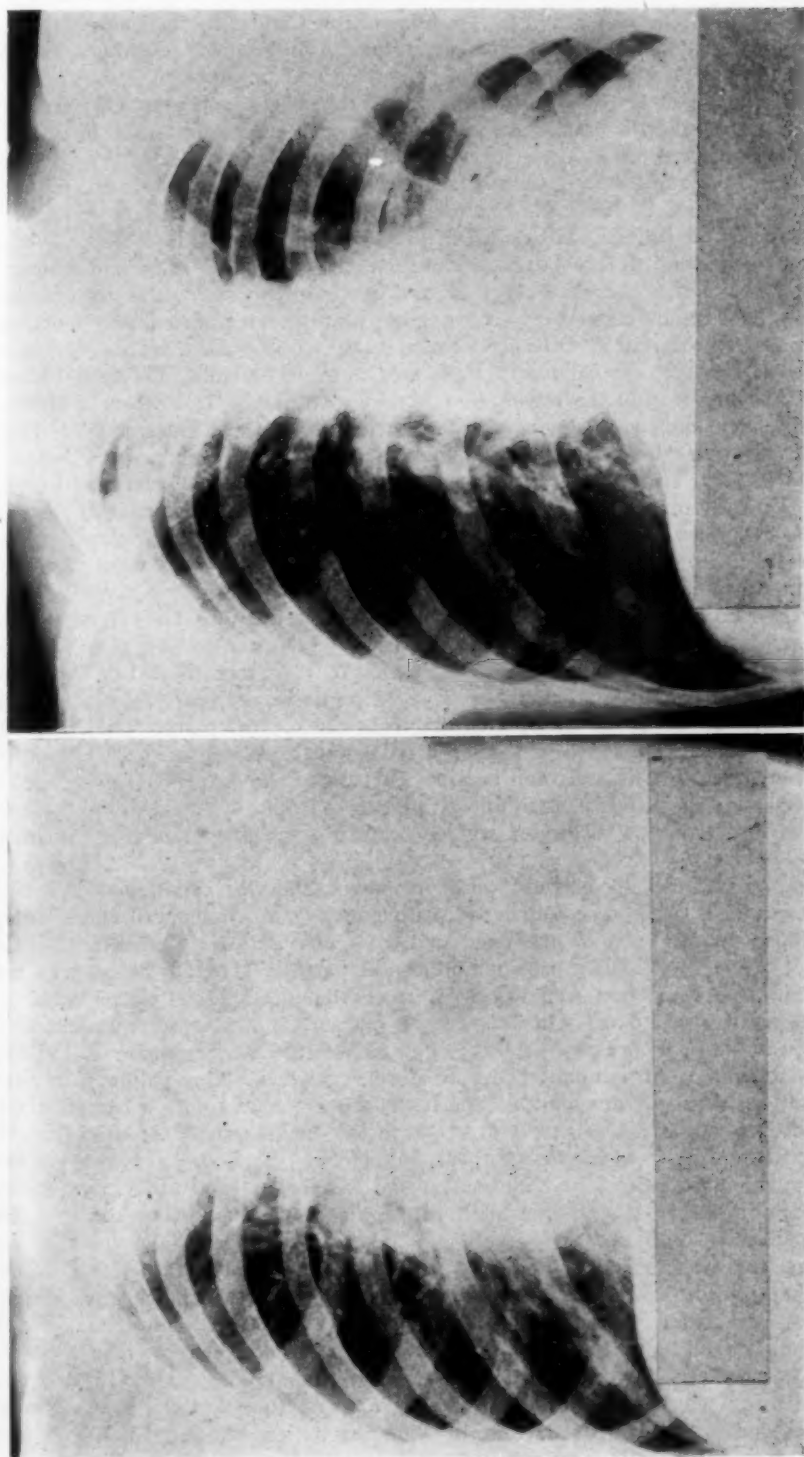


FIG. 1. Roentgenograms of case 3 (left, June 26, 1942; right, October 6, 1942). Onset of empyema about April 11, 1942. Five thoracenteses were done between June 26 and July 15, 1942. The last roentgenogram showed only a moderate degree of thickened pleura.

*Case 4*, aged 30, developed a lobar pneumonia on the right, was admitted to a station hospital on April 13, 1942 where he was placed on sulfathiazole therapy. On April 27 he developed an empyema on the right side and on April 30, 500 c.c. of a turbid fluid, which contained a beta hemolytic streptococcus and staphylococcus on culture, were removed by thoracentesis. On May 1, 850 c.c. and on May 5, 825 c.c. of a turbid seropurulent fluid were evacuated. On May 13, 600 c.c. of a thinner fluid were obtained by thoracentesis. Culture reports were not available for these latter three fluids. On June 9, 720 c.c. of a relatively thick, sterile, purulent fluid were aspirated. Again on June 12, 210 c.c. of a thinner fluid and on July 2, 350 c.c. of a seropurulent sterile fluid were obtained. The patient was acutely ill and had temperature as high as 103.8° F. between April 27 and 30, following which his temperature fell to below 100° F., and after May 18 his temperature became normal and remained so. When he was received at O'Reilly General Hospital July 24, there was evidence of thickened pleura at the right base but no free fluid was found. He soon became ambulatory and began to gain weight. A roentgenogram taken December 12 showed only slight residual thickened pleura, and he returned to full duty December 31, 1942.

*Case 5*, aged 34, developed pneumonia and was admitted to a station hospital December 31, 1942. He was placed on sulfathiazole therapy which he received intermittently. Date of onset of the empyema could not be exactly determined, but on January 29, 1943, 75 c.c. of a seropurulent sterile fluid were obtained by thoracentesis from the left chest. Again on March 4, 100 c.c. of a similar fluid were obtained. The patient had intermittent fever as high as 101° F. until February 6, 1943 when it fell and remained normal after February 10. He continued to have fluid in the chest and was admitted to O'Reilly General Hospital March 20, 1944. On April 5, 30 c.c. of a sterile rather thick fluid were evacuated by thoracentesis and on April 16, 75 c.c. of a similar fluid were obtained. The fluid on these two taps was rather thick and a small amount of saline was used to irrigate the pleural space. On April 21, 125 c.c. and April 23, 150 c.c. of a thinner sterile fluid were aspirated. During this period he remained afebrile and soon became ambulatory. By April 31 a roentgenogram showed only moderate pleural thickening and on June 6 this was minimal in amount. He was returned to limited service because of a polyglandular dysfunction on July 24, 1943.

*Case 6*, aged 25, developed an atypical pneumonia and was admitted to a station hospital January 25, 1943. The course of his illness was not serious until on February 1 he developed an empyema on the right and his temperature rose to 105° F. On February 3, 500 c.c. of a thin brown fluid containing 98,500 white blood cells per cu. mm. and a beta hemolytic streptococcus were evacuated. He was placed on sulfathiazole therapy on that date. On February 4, 500 c.c. of a thin seropurulent fluid were obtained, and on February 5, 800 c.c., February 6, 350 c.c., February 7, 150 c.c., and April 10, 100 c.c. of a thin sterile fluid were evacuated. This patient was very acutely ill at the onset of the empyema and had a stormy course with a bacteremia, a positive blood culture for beta hemolytic streptococcus on February 3 and February 4, acute nephritis and a severe anemia with hemoglobin of 33 per cent. However, following repeated thoracenteses his temperature fell to a lower level and patient began to show clinical improvement. In addition to the usual supportive therapy this patient received several transfusions. The patient continued to have fluid in the pleural space and was received at O'Reilly General Hospital May 1, 1943. On May 3, 150 c.c. of a thin brown sterile fluid containing 1950 cells of which 48 per cent were neutrophils were evacuated by thoracentesis. On May 5, 100 c.c. and on May 8, 130 c.c. of a similar fluid but containing only 180 white blood cells per cu. mm. were removed. Thoracenteses were continued, yielding May 12, 150 c.c., May 15, 450 c.c., May 17, 310 c.c., May 21, 325 c.c., May 27, 225 c.c. and June 4, 180 c.c. Following these repeated thoracenteses of thin sterile fluid the patient showed further clinical

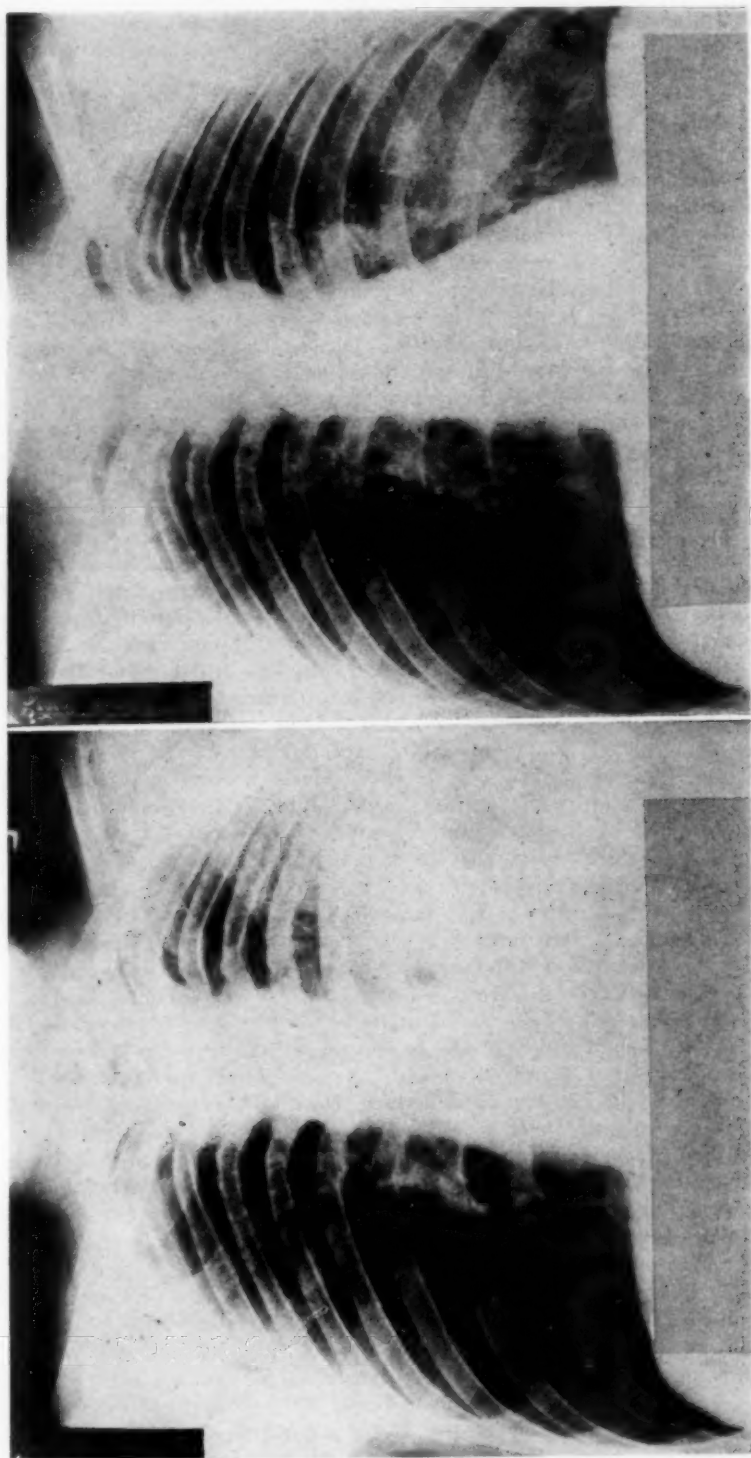


FIG. 2. Roentgenograms of case 5 (left, March 31, 1943; right, July 17, 1943). Onset of empyema about January 25, 1943. Four thoracenteses were done between April 5, 1943 and April 23, 1943. The last roentgenogram showed a minimal amount of pleural thickening.

improvement and by June 10 was afebrile, asymptomatic and ambulatory. Roentgenogram taken July 23 showed a moderate degree of residual thickened pleura. He returned to full duty August 6, 1943.

*Case 7*, aged 20, was admitted to a station hospital May 6, 1943 with what was apparently an acute upper respiratory infection and developed a lobar pneumonia on the left side on May 13, at which time sulfonamide therapy was begun. On May 18 he developed an empyema on the left. On May 25, 40 c.c. of a viscid sterile fluid containing 3,050 white blood cells per cu. mm. with 100 per cent neutrophils were evacuated by thoracentesis. His temperature which had been elevated to around 102° F. promptly fell to 100° F. A considerable amount of fluid remained in the chest, but the patient remained relatively asymptomatic until in August his temperature again became elevated to as high as 102° F. for a period of about a week. He was admitted to O'Reilly General Hospital August 26, 1943 and was placed on sulfadiazine therapy. On September 2, 450 c.c. of sterile seropurulent fluid were evacuated. On September 8, 450 c.c. and on September 19, 150 c.c. of a thinner sterile fluid were obtained. Shortly thereafter he became afebrile and ambulatory and on November 4 a roentgenogram showed only moderate pleural thickening. He was returned to temporary limited duty December 4, 1943 with the expectation that he would revert to full duty within a period of three months.

*Case 8*, aged 35, was admitted to a station hospital December 27, 1943 with what was apparently an acute upper respiratory infection, and developed an atypical pneumonia January 19, 1944. He received sulfonamides intermittently and on February 4, 1944 he developed an empyema on the right and had an intermittent elevation of temperature as high as 102° F., but usually below 100° F. On March 9, 20 c.c. of a thick green pus containing a type XII pneumococcus was evacuated by thoracentesis from the right chest. The temperature returned to normal and on March 23 he was received at O'Reilly General Hospital at which time he was afebrile and ambulatory. Examination demonstrated that there was no free fluid present in the chest but only some thickening of the pleura which showed considerable clearing by roentgenogram on April 28. He was returned to limited duty on May 17, 1944 with the expectation that he would revert to full duty within a period of three months.

*Case 9*, aged 18, developed scarlet fever and was admitted to a station hospital January 10, 1944. During the course of scarlet fever he developed bilateral bronchopneumonia for which sulfonamide was prescribed, but on January 19 he developed empyema in the left chest. On January 20, 650 c.c. of seropurulent fluid with specific gravity of 1.020, showing beta hemolytic streptococcus on culture, were evacuated by thoracentesis. On January 22, 360 c.c., January 23, 690 c.c., January 26, 120 c.c. of sterile fluid were aspirated. Following initial thoracentesis the temperature dropped to 100° F. or below, and by February 9 it became normal. He was received at O'Reilly General Hospital March 30, 1944. Examination at that time showed only a slight amount of thickened pleura and he was placed on an ambulatory regimen and returned to full duty May 9, 1944.

*Case 10*, aged 19, developed atypical pneumonia and was admitted to a station hospital February 6, 1944. On February 25 he developed an empyema on the left and was started on sulfadiazine which was continued until March 4. On February 28, 500 c.c. of turbid fluid which showed a beta hemolytic streptococcus on culture were evacuated by aspiration from the left chest. On March 1 he was started on penicillin intramuscularly and continued until March 15. On March 2 a small amount of turbid fluid containing beta hemolytic streptococcus was aspirated and 10,000 Oxford units of penicillin were injected into the left pleural space. On March 5 and on March 7 unspecified amounts of sterile fluid were evacuated from the left chest. Following this latter aspiration his temperature fell to below 100° F., and became normal after March 16. This patient was very acutely ill for about a week and in addition to the

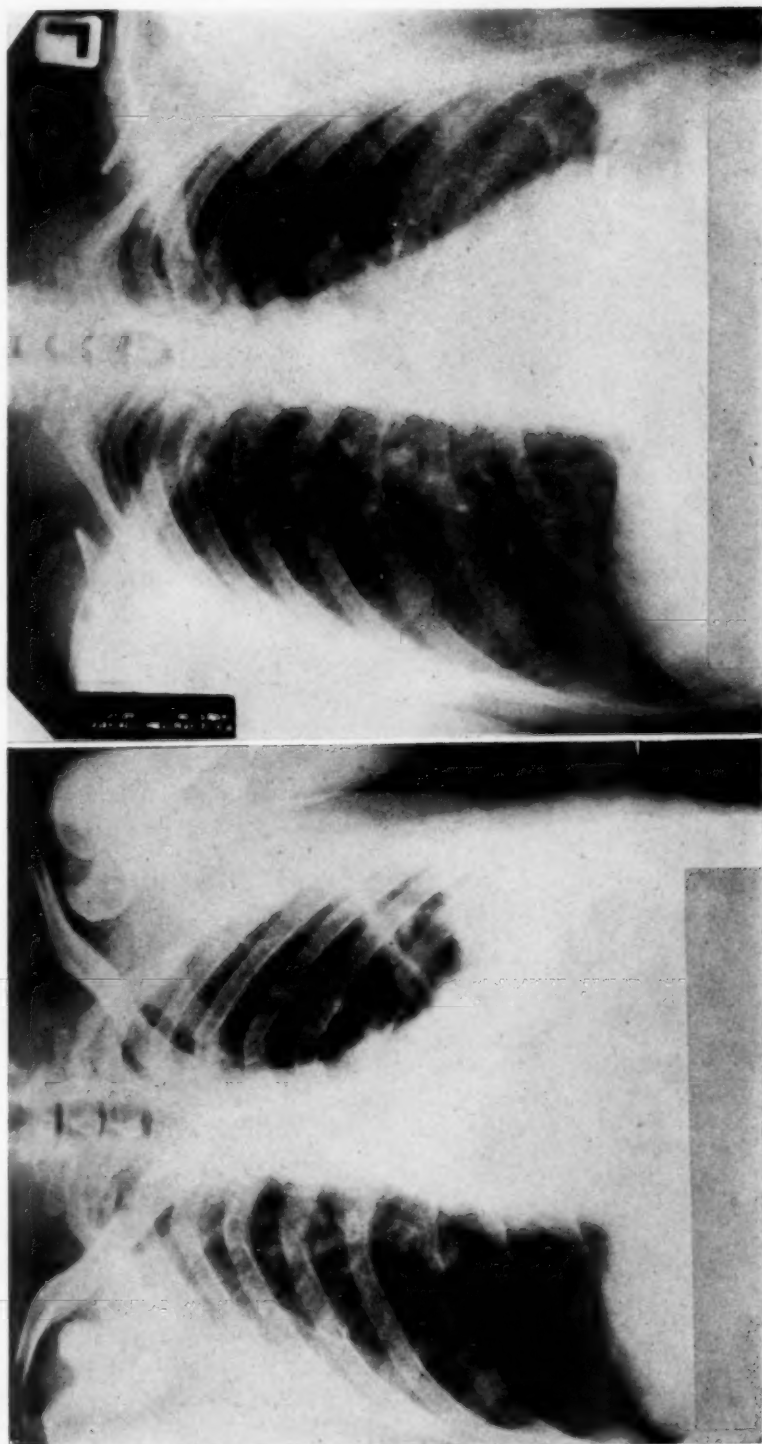


FIG. 3. Roentgenograms of case 12 (left, November 13, 1944; right, November 30, 1944). Onset of empyema November 10, 1944. Four thoracenteses were done between November 13 and November 16, 1944. The last roentgenogram showed minimal amount of pleural thickening.

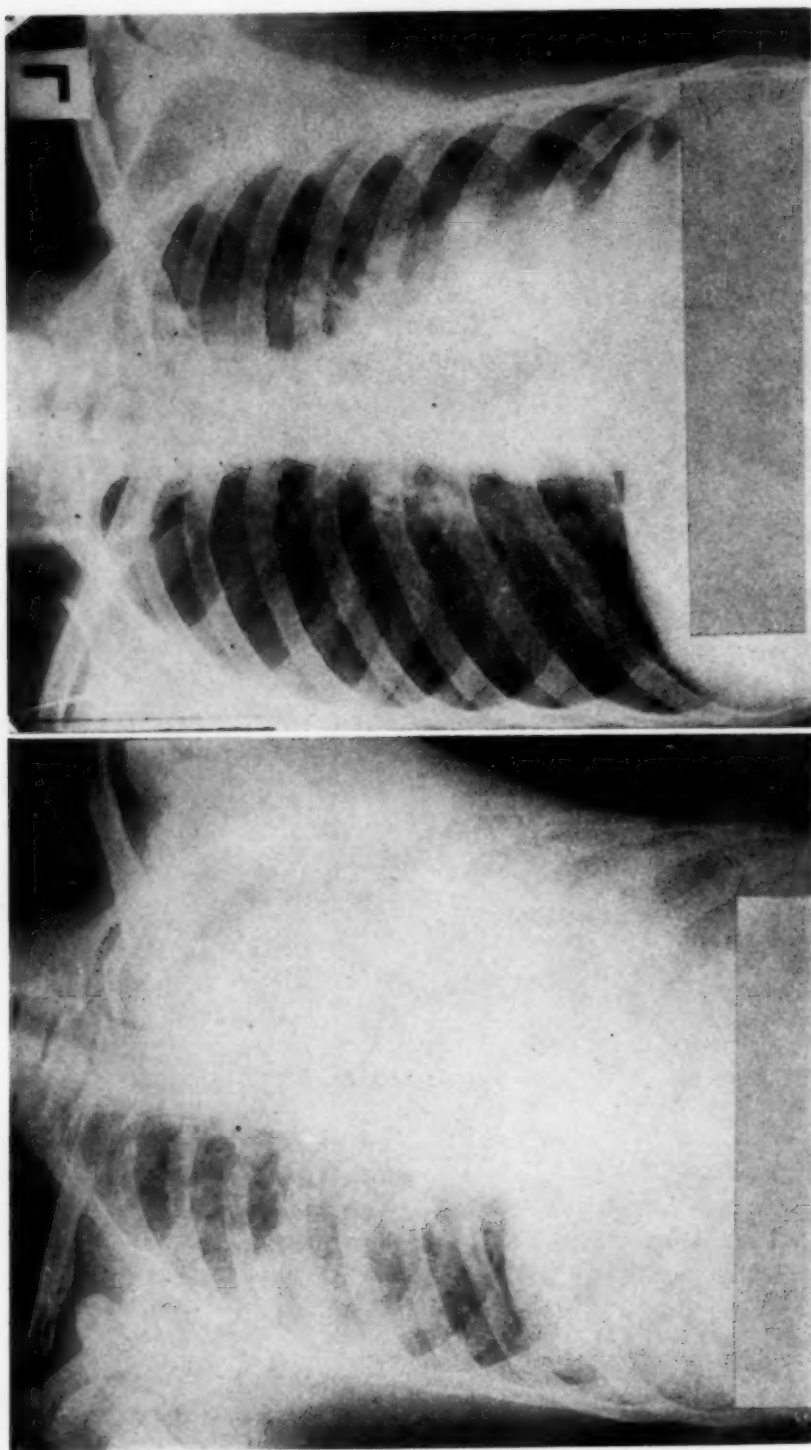


FIG. 4. Roentgenograms of case 13 (left, April 17, 1945; right, May 15, 1945). Onset of streptococcus bronchopneumonia and empyema on the left on April 16, 1945. The shadow on the left side in the roentgenogram of May 15, 1945 represents pleural thickening only.

usual supportive treatment he received three blood transfusions. He was received at O'Reilly General Hospital April 3, 1944 at which time he was ambulatory and afebrile, and roentgenogram of the chest showed only minimal amount of pleural thickening. He returned to full duty May 30, 1944.

Case 11, aged 21, was admitted to O'Reilly General Hospital from the command March 28, 1944 with atypical pneumonia. He was placed on sulfadiazine therapy,

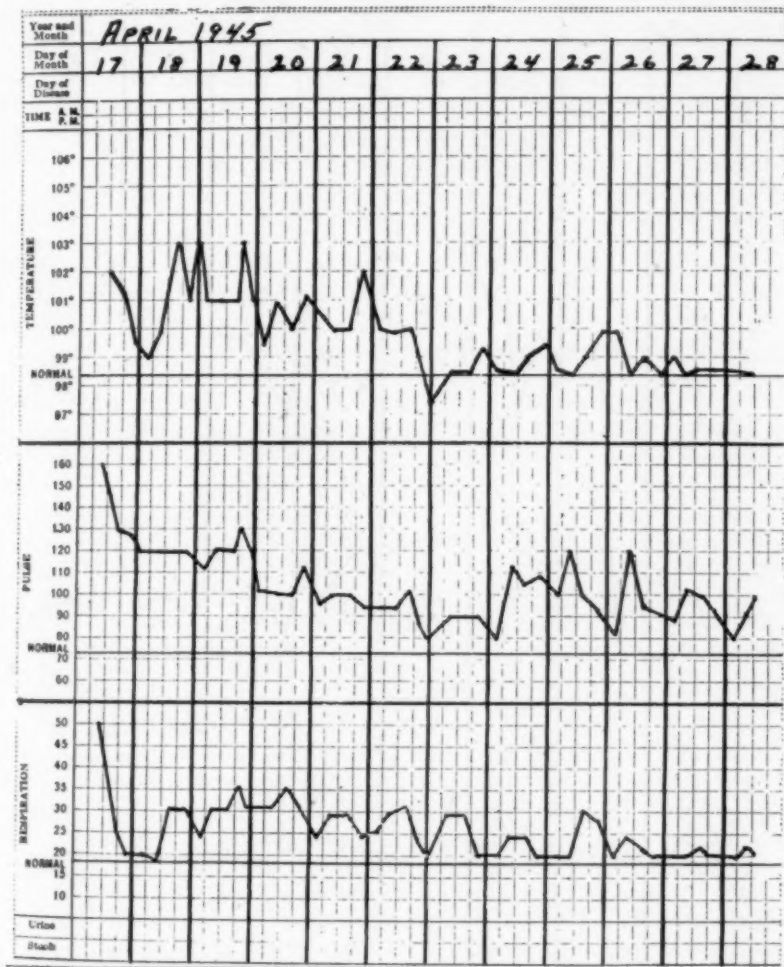


FIG. 5. Temperature curve of case 13. Onset of empyema April 16, 1945.

but on April 2 he developed an empyema on the left side. On April 4, 75 c.c. of sterile seropurulent fluid containing 6,400 white blood cells per cu. mm. were evacuated from the left chest. On April 8, 20 c.c. of a thinner sterile fluid were aspirated, and the temperature returned to a normal level. He became ambulatory, and on April 14 a roentgenogram of the chest showed only minimal pleural thickening which cleared almost entirely by April 21, and he returned to duty April 30, 1944.

Case 12, aged 25, a sailor on furlough was admitted October 9, 1944 to O'Reilly General Hospital with type II pneumonia of the left lower lobe. He was placed on

sulfadiazine for five days and his temperature returned to normal level within 24 hours, but there was a slow resolution of the pneumonic process. On November 10, 1944 he developed an empyema on the left side and sulfonamide therapy was again started. On November 13, 800 c.c. of a cloudy sterile seropurulent fluid containing 5,600 white blood cells per cu. mm. and having a specific gravity of 1.023 were obtained by thoracentesis from the left chest. On November 14, 750 c.c., November 15, 500

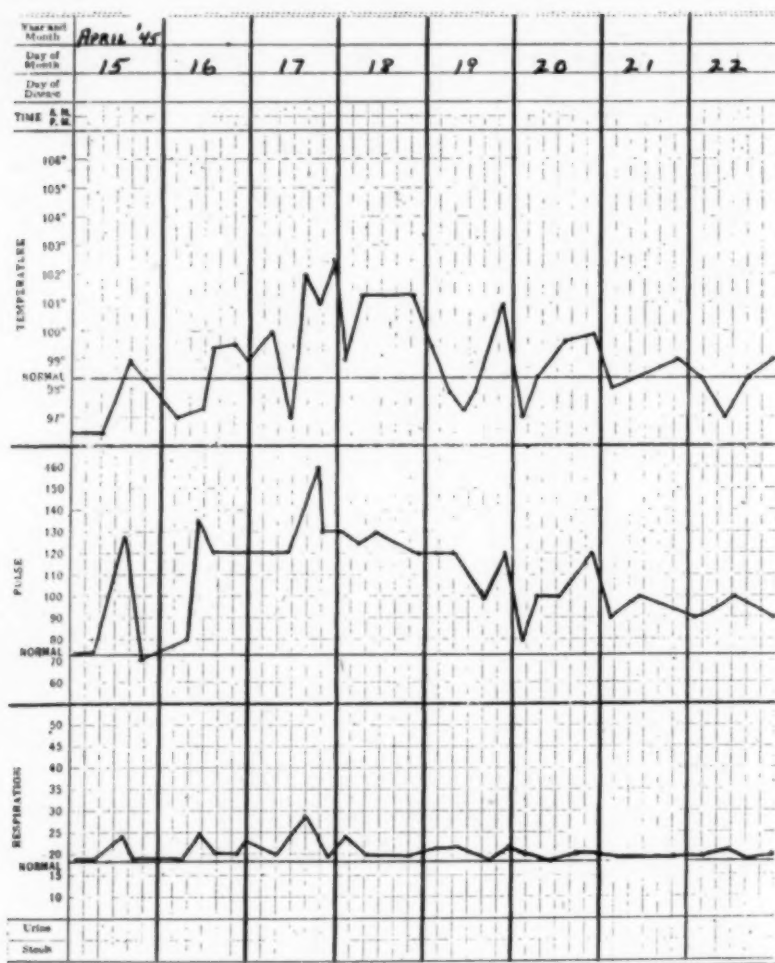


FIG. 6. Temperature curve of case 14. Onset of empyema April 17, 1945. Temperature remained normal after April 22, 1945.

c.c., November 16, 250 c.c., of thin, cloudy, sterile fluid were aspirated. His temperature was elevated only slightly for three days with the empyema. He was never acutely ill, he became ambulatory about December 1, 1944 and returned to a furlough status December 8, 1944.

Case 13, aged 19, developed scarlet fever while on furlough on April 10, 1945 and was placed on small doses of sulfadiazine. On April 16 he became acutely ill with symptoms of acute pulmonary infection, and was admitted to O'Reilly General

Hospital April 17. On admission he was severely ill with temperature 102° F., pulse 160, respirations 50, deep cyanosis and considerable dehydration. He was found to have bilateral bronchopneumonia and empyema on the left and was immediately placed in an oxygen tent. Intravenous sulfadiazine and intramuscular penicillin therapy were initiated. A thoracentesis was promptly done and 1,000 c.c. of a turbid brownish fluid with specific gravity of 1.022 were obtained. This fluid contained 13,750 white blood cells per cu. mm. with 99 per cent neutrophils and beta hemolytic streptococcus was found on culture. Forty thousand units of penicillin were instilled into the pleural space. On April 18, 250 c.c. of a lighter colored sterile fluid with specific gravity of 1.020 and containing 11,000 white blood cells per cu. mm. were obtained, and again 40,000 units of penicillin were instilled into the pleural cavity. Further thoracenteses were done with the following results: April 20, less than 10 c.c.; April 23, 160 c.c. of a thin sterile fluid with specific gravity of 1.015 and 3,300 white blood cells per cu. mm.; April 28, 35 c.c. of brown sterile fluid with specific gravity of 1.022; April 30, 30 c.c.; May 4, 40 c.c.; May 10, 30 c.c. The fluid obtained on the last three taps contained some blood and increased numbers of white blood cells and the specific gravity was as high as 1.030. Promptly following the first thoracentesis there was marked clinical improvement with considerable clearing of the cyanosis and reduction of the temperature, pulse and respiratory rate. By April 22 the temperature fell to below 100° F., the patient began to regain his appetite and strength, and by April 29 the temperature fell to normal. Penicillin was discontinued and he was allowed out of bed on May 9. Sulfadiazine was continued until May 15. On May 15 roentgenogram of the chest showed only moderate residual pleural thickening on the left. On May 18 temperature rose to 103° F. for 12 hours and the patient had what was probably a mild recrudescence of the pneumonia. Sulfadiazine was again given, and he became asymptomatic after 48 hours.

Case 14, aged 27, was originally admitted to this general hospital March 10, 1945 because of repeated attacks of left hemiparesis. The neurological service determined that he had an intracerebral aneurysm, and ligation of the right common carotid artery was done March 29. Three days later he developed pneumonia at the right base with later involvement of the left lower lobe. He was placed on sulfonamide therapy and on April 11 intramuscular penicillin therapy was begun. On April 18 he developed an empyema on the right and on April 19, 450 c.c. of sterile sero-sanguineous fluid were aspirated. This fluid contained 8,350 white blood cells with 85 per cent neutrophils per cu. mm., and had a specific gravity of 1.018. On April 19, 450 c.c. of a similar sterile fluid were aspirated, April 21, 600 c.c. of a similar fluid containing 2,250 white blood cells per cu. mm., April 22, 600 c.c. of a similar fluid, and on April 23 a thinner fluid containing practically no white blood cells was obtained by thoracentesis. Further attempts at aspiration failed to produce any fluid. On April 20 the patient's temperature fell to below 100° F., and by April 29 it became normal. Penicillin was continued until May 8 and sulfadiazine continued until May 14. On May 11 roentgenogram showed evidence of a moderate amount of thickened pleura and an elevated diaphragm on the right side. By May 15 the patient was asymptomatic as far as the chest was concerned and was transferred back to the care of the neurosurgical service.

#### DISCUSSION

It appears from our experience that postpneumonic empyema, when the infecting organism is a pneumococcus, staphylococcus or streptococcus, can be successfully treated by the use of sulfonamides, penicillin and repeated thoracenteses. Sulfonamides alone when given by mouth or intravenously

in conjunction with thoracentesis resulted in a rapid sterilization of the exudate in 11 cases. In addition, three cases received penicillin therapy. In some of our cases the exudate was found to be sterile at the time of the first aspiration, but it is our feeling that because the fluid obtained in these cases was turbid and highly cellular they were originally infected and became sterilized even before thoracentesis was done. Further contributory evidence to such a view is shown in one of our cases (case 1) in which a short chain streptococcus was found on the smear of the pleural exudate but failed to grow on culture. Following the initial aspiration and sterilization of the pleural exudate the patients in most instances showed considerable improvement and the temperature shortly fell to below 100° F. In a few cases further aspiration was necessary before the temperature fell to a lower level. In the cases in which the thoracenteses were repeated at sufficiently frequent intervals the course of the patient was that of a relatively rapid clinical recovery. In nine of these cases thoracenteses were done early and at intervals of sufficient frequency until no further fluid was formed, and the course of their illness was most satisfactory. The pleural exudate obtained in successive thoracenteses in these cases showed a diminishing turbidity and viscosity and a decreasing number of white blood cells and at final evacuation was practically serous in character. The length of time following initiation of thoracenteses to the point at which no further fluid formed varied considerably in these nine cases. One case required only one thoracentesis and one required only two. The most severely ill of any of these cases (6) required 15 thoracenteses over a period of four months. In practically all of these cases the patients became completely afebrile in a short period of time, rapidly became asymptomatic and developed a normal appetite. The end result in all of these cases was complete reexpansion of the lung, only a minimal amount of pleural thickening and no permanent disability resulting from the course of the pneumonia and empyema.

In evaluating the length of illness of these cases the total length of hospitalization can in no way be compared to that generally seen in civilian practice. It must be remembered that when a soldier is discharged from a hospital he is expected to perform any duty assigned to him, including full field duty. In all but four of our cases a prolonged period of convalescence and a period of three or more weeks was spent on furlough or in a reconditioning unit before he was declared fit for duty and discharged from the hospital. In comparison with a group of 12 cases handled under similar military conditions in this general hospital by the usual thoracostomy method of treatment, this group of cases treated by repeated thoracenteses compares more than favorably in the length of time assigned to the hospital.

Five of our cases (3, 4, 5, 7, 8) were not handled throughout their course as, in the light of our present knowledge, we think would have been most beneficial. Thoracentesis had been delayed or not repeated at sufficiently frequent intervals and the pleural exudate had become somewhat thickened

before admission to this general hospital. The question naturally arises as to whether or not thoracostomy would have been the desirable method of approach at that time. However, in one case (8) only thickened pleura remained and in the others repeated aspirations succeeded in removing all of the remaining fluid, which became increasingly thinner on repeated evacuations, and the patients convalesced rapidly after the exudate had been completely removed. We doubt seriously if at the time these cases were received they would have recovered as rapidly with thoracostomy as with simple multiple aspirations. In cases of rather longstanding empyema it is well known that both the parietal and visceral pleura are covered with a thick serofibrinous exudate. If thoracostomy is done in such a case a cavity between the visceral and parietal pleura inevitably results. The size of this cavity depends on the amount of pleural space which had been occupied by the exudate and the ability of the lung, which is already at least partially tied down by exudate and semifibrinous adhesions on the visceral pleura, to re-expand. As time goes on and the exudate on the visceral pleura becomes more fibrinous the ability of the lung to re-expand is decreased and the cavity within the pleural space either fills in slowly or not at all. A further factor which would tend to decrease the ability of the lung in such cases to re-expand is the disturbance of normal intrathoracic pressures produced by the thoracostomy. It is in this type of case that secondary operations designed to collapse the rib cage or to decorticate the lung have been found to be necessary. The picture of the chronic postoperative empyema case with a large cavity, not infrequently secondarily infected, and requiring multiple surgical procedures is a discouraging one to both patient and physician. From past experience we feel that some of our cases could have developed such a picture if thoracostomy had been performed. In contrast to this the evacuation of the pleural exudate by repeated thoracenteses brings the visceral and parietal pleura into apposition and a true cavity within the pleural space is never formed. As the visceral and parietal pleura come into apposition they adhere to each other and contraction produced by the formation of fibrinous adhesions, far from preventing the re-expansion of the lung, has the effect of producing re-expansion. In addition when no actual cavity is formed within the pleural space with an opening through the chest wall the normal pressures within the pleural cavity are maintained and normal respiratory motion continues to have the effect of expanding the lung. Also secondary infection with such sulfonamide and penicillin resistant organisms as the pyocyanous bacillus and *Proteus vulgaris* has little opportunity to occur when thoracenteses only are performed. The amount of residual pleural thickening which occurs is certainly no greater than that after thoracostomy.

In the management of postpneumonic empyema by this method adequate sulfonamide dosage intravenously or by mouth should be given throughout the course to maintain a blood level of between 5 and 8 mg. per cent, always observing the usual precautions in regard to possible sulfonamide complica-

tions. Our experience with penicillin has been limited to three cases (10, 13, 14), but in one case (10) the pleural exudate was not sterilized after five days on sulfonamide and rapidly became sterile after intrapleural injection of penicillin. It certainly appears that it would be advisable, where the effecting organism is suspected of being penicillin sensitive, to instill that drug into the pleural space until the exudate becomes sterile. Whether further injections are advisable may be questionable, as it is possible that the drug may have an irritating effect on the pleura as it apparently does on the meninges.<sup>9</sup> In none of our cases was sulfonamide used locally. It is most important that the initial thoracentesis be done early in the course of empyema whether the disease accompanies or follows the preceding pneumonia. Every attempt should be made completely to evacuate the pleural space initially as far as practicable. Amounts up to 1000 c.c. can be removed with safety, but generally if the taps are done promptly considerably less fluid will be obtained. Thoracentesis with complete evacuation of the exudate should be repeated at frequent intervals of one or more days as the exudate reforms and should be continued until no further fluid is found. Complete examination, including smear, culture, cell count and specific gravity, should be made on each specimen. Although small amounts of sterile serous fluid may be reabsorbed, the removal of all such fluid as far as practicable enhances the convalescence of the patient and decreases the formation of pleural adhesions. All means available should be used accurately to locate any pleural exudate. Careful physical examination, roentgenograms with the usual technic and the Potter-Bucky technic, fluoroscopic examination and exploratory aspirations all have their usage. Thoracentesis should be done with the usual precautions by a closed method. Replacement of removed fluid with air was not done in our cases, but on several occasions small amounts of air inadvertently escaped into the pleural space without any deleterious results. Where small amounts of thin fluid remain in the pleural space the careful injection of about 25 c.c. of air may be of aid in localizing any remaining fluid.

Admitting that 14 cases is a small series upon which to base any definite conclusions, the course of these cases, and others reported in the literature, has led us to the belief that a procedure different from the generally accepted surgical method of handling postpneumonic empyema should be considered. In addition to the four cases reported by Keefer and his associates,<sup>5</sup> Blades and his co-workers<sup>10</sup> in a recent report of 24 cases of thoracic empyema found that three cases were apparently cured by the use of repeated thoracenteses without thoracostomy. These latter authors were of the opinion that if thoracenteses had been more assiduously employed a greater number of their cases would have recovered without operation. Our recommendation is that postpneumonic empyema caused by organisms susceptible to sulfonamide and penicillin therapy should be treated by the continued use of these drugs and early and frequently repeated thoracenteses until no further

exudate is present in the pleural space. The exudate should not be allowed to form thick pus. Where such procedures can be successfully carried out thoracostomy should not be necessary. In certain instances the pleural exudate may be encapsulated in an area which precludes safe and adequate drainage by thoracentesis and in such cases the surgical approach would be necessary.

#### SUMMARY

1. Fourteen cases of postpneumonic thoracic empyema were successfully treated without complication by the use of sulfonamides, penicillin and multiple thoracenteses.

2. When thoracentesis was done early in the course of the empyema and was frequently repeated the pleural exudate, which was rapidly sterilized, became less purulent and more serous in character and could be completely evacuated.

3. From these clinical observations we feel that this method should be routinely applied in postpneumonic empyema. The previously accepted procedure of allowing the pleural exudate to become thickened and performing a thoracostomy should be applied only when thoracentesis cannot be safely used because of the location of the exudate or where the infecting organism is resistant to sulfonamides and penicillin.

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## THE EARLY DIAGNOSIS OF FILARIASIS AND CERTAIN SUGGESTIONS RELATIVE TO CAUSE OF SYMPTOMS \*

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FILARIASIS has long been characterized by the physical findings of elephantiasis, lymphadenitis, marked physical deformity, and by the demonstration of microfilariae on blood smear. These features are indicative of a "late stage" of filariasis. The military necessity for occupation of filarial endemic areas has afforded an opportunity to study the "early stages" of filariasis. The syndrome of early filariasis has been outlined by Wartman and King,<sup>1</sup> and by various medical officers who have recently returned from the area in which filariasis is endemic. Since September of 1943, we have had an opportunity to study the "early stages" of filariasis. All patients included in this survey came from islands in the South Pacific areas on which filariasis was known to be endemic both from a clinical examination of the natives and by demonstration of microfilariae in the blood smear of these natives. It will be shown that by careful review of symptoms, physical examination, and laboratory findings, it is possible to make a definite diagnosis of filariasis prior to the development of the formerly accepted criteria for this diagnosis.

The patients considered in this study are a group of 100 soldiers evacuated from widely separated areas in the Southwest Pacific. The average age of the group was 26.6 years. The average time spent in endemic areas prior to the development of symptoms of filariasis was 13.3 months. The number of months from the time of entry into the endemic areas to our observation was 16.3 months. Our period of observation averaged 7.3 weeks.

In establishing the diagnosis of filariasis, the following factors were considered: (1) The residence and length of stay in areas where filariasis is known to be present; (2) the history of symptoms associated with the early stages of the disease; (3) the clinical findings; (4) the results of local reactions to skin tests performed with filarial antigens; and (5) the clinical course subsequent to the onset of symptoms. It is felt that these cases were without doubt individuals who harbored the filarial parasite. However, in but two of our cases were microfilariae demonstrated on blood smear. In other soldiers evacuated from the same areas and with the same symptoms, the adult worm had been demonstrated in biopsies performed elsewhere (Wartman and King<sup>1</sup>). Of particular interest is the fact that the chain of

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symptoms will vary from area to area, and that in many cases the subjective symptoms were rather marked although the physical findings were rather meager. The reverse was also found to be true. Unless one is familiar with the syndrome of "early filariasis," a great many of these cases would in all probability be considered to be functional in origin. The existence of a skin test which has a fairly high degree of specificity is an added objective aid in the diagnosis.

### SYMPTOMS

The earliest symptom in the usual case of filariasis is pain in the scrotal area which is characterized by a feeling of weight and a dull, aching sensation localized to the testicles or to the structures immediately above the testicles. Frequently associated are symptoms of nausea, anorexia, and of deep-seated, generalized aches and pains in the back, arms, and legs. The pain in the legs is commonly found to follow the adductor canal. That in the arms is more generalized and has no characteristic distribution. Backache is predominantly lumbar in location.

TABLE I  
Symptoms and History of:

| Symptom                                  | % of Occurrence |
|--|-----------------|
| Lymphadenitis.....                       | 63              |
| Swelling in scrotum.....                 | 61              |
| Pain in testicles.....                   | 50              |
| Generalized aches and pains.....         | 42              |
| Nausea and anorexia.....                 | 35              |
| Pain in arms and legs.....               | 26              |
| Lethargy, malaise, and fatigability..... | 22              |
| Lymphangitis.....                        | 19              |
| Symptoms with work.....                  | 15              |

Coincident with these symptoms, the individual will frequently observe the development of a rather generalized lymphadenopathy and palpable swelling of the scrotal contents. Lethargy, fatigability, and an increase of all the symptoms on exertion are frequently noted. Lymphangitis is a common occurrence, but was present in only 19 per cent of this series. It is of particular interest to note that in certain areas the individual's first awareness of systemic disease is the accidental finding of an enlargement of the scrotal contents. The subjective symptoms are prone to develop suddenly, are mild to moderate in severity, and are subject to remissions and exacerbations. The frequency of occurrence of symptoms is noted in table 1.

### PHYSICAL FINDINGS

Our evaluations of the frequency of various findings must be interpreted in the light of the fact that physical findings in early filariasis are not constant. It has frequently been noted during our period of observation that lymph nodes may vary remarkably in size and that an acutely enlarged gland may diminish in size in a few weeks. Likewise, these patients fre-

quently stated that the degree of funicular enlargement had been much greater at some time in the past. The lymph node involvement was primarily axillary, cervical, and epitrochlear. Inguinal lymphadenopathy was usually discounted unless unquestionably enlarged, as the same degree of lymphadenopathy in this area is frequently to be observed in soldiers returning from tropical service. Lymphadenopathy has not infrequently been found in such unusual areas as the antecubital space and in the intercostal spaces low in the midaxillary line, the latter having been proved by biopsy. The finding of enlarged epitrochlear glands is especially significant. The glands are firm, discrete, and characteristically somewhat tender to pressure. Examination of the scrotal contents may reveal a large firm tender testicle or thickening of the epididymis or enlargement of the funiculus. The latter may present the physical findings of a varicocele with soft, dilated, easily movable veins or an inseparable thickening of all structures of the spermatic cord. Funiculitis is one of the most permanent of all physical findings. Whenever involvement of this structure had been noted at some time in the past, ab-

TABLE II  
Clinical Findings on Our Examination

| Findings             | % of Occurrence |
|----------------------|-----------------|
| Lymphadenopathy..... | 92              |
| Funiculitis.....     | 77              |
| Orchitis.....        | 20              |
| Local edema.....     | 7               |
| Lymphangitis.....    | 4               |

normality was still obvious on our examination. This, however, was not true with respect to lymph node involvement. Lymphangitis was infrequent in our experience. One individual, however, experienced repeated bouts of lymphangitis. Each episode was confined to the same area in the forearm and was associated with fever and systemic symptoms which would disappear completely within a week. The frequency of occurrence of physical findings is noted in table 2.

#### LABORATORY EXAMINATION

No characteristic abnormalities were noted on routine laboratory examination. Eosinophilia was not noted. Microfilariae were demonstrated once in our hospital in an individual who had lived for years in an endemic zone in childhood. In another patient, microfilariae were demonstrated in an overseas hospital. Dr. John Bozicevich of the National Institute of Health, Bethesda, Maryland, demonstrated to us the use of a skin test and furnished filarial antigens for the skin testing of all these patients. A detailed description of the skin test, its limitations and specificity will appear presently in a paper by Dr. Bozicevich. The materials used for the testing were a 1/8000 dilution of antigen prepared from the horse filarial worm and the dog heart worm. Both a dog and a horse protein control as well as a saline control were used. In the present series, 88 per cent showed positive

skin reactions whereas 12 per cent were negative. Controlled studies in 49 normal non-allergic individuals who had not been in endemic zones indicated the occurrence of approximately 10 per cent false positive reactions. Studies on 50 allergic individuals from the northern United States without tropical service revealed the presence of 14 per cent false positives. These figures compare favorably with those reported by Wartman and King<sup>1</sup> (90 per cent positive in known cases of filariasis and 10.5 per cent positives in controls) and of those of Bozicevich (to be published).

#### PROGRESS AND COURSE OF DISEASE

At the time of admission, most of these soldiers were relatively symptom free. Some complained of generalized aches and pains, persistence of fatigue, and discomfort in the testicular and funicular structures. The majority of these patients were transferred to a reconditioning unit where approximately 25 per cent complained of increased pain and discomfort in direct proportion to the severity of physical activity of the training. It was found that hot showers and high environmental temperatures frequently caused a transitory exacerbation of symptoms. In a few individuals definite changes in physical findings were observed. One soldier carried a heavy barracks bag approximately one-third of a mile and complained of sharp pain in the funicular area. Within a matter of four hours the funicular structures had trebled their size, were tense, and exquisitely tender. This subsided to the previous level within five days of bed rest. In several others, unquestionable enlargement of lymph nodes occurred following physical activity. In general, however, continued physical training over a period of three to four weeks resulted in progressively fewer complaints. Although periodic recurrences of systemic symptoms were noted, these became less severe.

#### CONSIDERATIONS REGARDING THE MECHANISM RESPONSIBLE FOR SYMPTOMS

The exact anatomical and physiological basis for production of symptoms is unknown. Mechanical blockage by the parasite undoubtedly is a prominent factor in the late and irreversible stages of the disease. The rapid appearance and subsidence of lymphangitis, lymphadenitis, and funicular enlargement suggests a less permanent and more readily reversible cause. In this connection, an inflammatory or an allergic response bears consideration. In the early cases the former has not been demonstrated. In this study there have been several factors suggesting that these responses may be allergic in their origin. This was first brought to our attention by the occurrence of a cyclically recurring erythema in an individual, who, following intradermal skin test with the horse antigen, presented an erythematous reaction in the skin test site each afternoon for a period of five days. This same occurrence although less intense and lacking in periodicity has

been noted in several other patients. In one individual this occurred over a period of several weeks. Certain types of filariasis are characterized by the periodicity of appearance of microfilariae in the blood stream. These observations suggested that periodically there existed in the circulating blood a material to which the skin test area had been sensitized. This suggested an Arthus type of reaction to a circulating antigen. It is not difficult to assume that a similar reaction might well occur in internal organs or in glands or in funicular structures and be responsible for both symptoms and physical findings. The skin test itself appears to be a measure of local sensitivity to tissues sensitized by the filarial antigen. Allergic responses in general are characteristically sudden in onset, frequently rapid in subsidence with complete or almost complete reversibility of local tissue changes. After repeated allergic insults a particular tissue may show residual inflammatory infiltration and fibrosis. The evanescent nature of the initial symptoms, the occasional rapid appearance and disappearance of physical findings, the occurrence of symptoms under activity when microfilariae might mechanically be discharged from the parent worm and the reported occurrence of eosinophilia during acute exacerbations suggest that these may well be on an allergic basis. Were mechanical blockage of lymph channels responsible for these symptoms, such transient and reversible reactions would not be expected. It has been quite well established by Wartman, King and others that an acute pyogenic process is not present in these early cases and it would, therefore, appear that an allergic response to the filarial antigen may be responsible for many of the symptoms and physical findings of early filariasis.

#### DISCUSSION

There is no one constant chain of symptoms by which the diagnosis of filariasis can be made. There is considerable variability in these initial symptoms depending upon the area in which infection takes place. In certain areas the disease is ushered in by a variety of complaints including lethargy, fatigability, generalized aches and pains, anorexia, and digestive disturbances, whereas in other areas a few hundred miles away, these symptoms are conspicuous by their absence, and the first indication of disease is the accidental finding of a funicular enlargement. In general, however, the following may be considered as the average clinical history and physical findings. After a period of approximately one year in an endemic zone the individual is likely to experience mild, generalized aches and pains, testicular pains, malaise, and systemic symptoms of an infection, and at about the same time, a more or less generalized lymphadenopathy and a funiculitis will be observed. The occurrence of lymphangitis is of great diagnostic importance, but is frequently absent. The incubation period in our series varied from two to 22 months and is undoubtedly related to the density of filarial infestation in the area and to the degree of nocturnal exposure to mosquito bites. This was found to vary considerably on different islands, but was relatively constant

on any one particular island. The fact that microfilariae are infrequently found in the blood stream of these soldiers is not surprising, as Byrd and St. Amant<sup>2</sup> in a survey of the native population in American Samoa state that microfilariae are rarely found in the blood stream under five years of age, and that advanced physical findings of filariasis rarely develop before the twentieth year of life. We have examined a group of individuals who have spent considerable time in filarial areas and who were evacuated to the United States for reasons other than filariasis. These examinations and skin tests have been entirely negative suggesting that they either escaped the infection entirely or were so minimally infected that neither clinical symptoms and physical findings, nor cutaneous hypersensitivity could develop. The fact that once removed from an endemic area these soldiers do not experience frequent recurrence of symptoms and further that they showed regression and not progression of physical findings indicated that reinfection and probably also density of infection influences the time of occurrence, the severity and extent of symptoms and physical findings, and the clinical course of the disease. The life span of the adult worm and the length of survival of microfilariae are unknown. These undoubtedly have a rather definite limit of survival and it is reasonable to expect that in the course of time and in the absence of reinfection the symptoms of filariasis should diminish. From our observation of these patients during their period of hospitalization and from a number of follow-up letters, this concept would appear to be substantiated.

The primary reason for the early diagnosis of filariasis and the importance of recognizing the early manifestations lies in the province of preventive medicine. It is felt that early evacuation from an endemic zone will permit the disease to subside or possibly to disappear completely before irreversible changes occur. It is likewise important to recognize the early symptoms of the disease and their variability as many of these individuals would otherwise be considered as having functional disorders and might thus be denied the benefits of early evacuation to a non-filarial area. There is at present no certainty that avoidance of reinfection will prevent progression of the disease or the occurrence of complications at some later date. However, at present the evidence clearly indicates that in the early stages at least, avoidance of reinfection or removal to a temperate climate or both has resulted in a diminution in the frequency and severity of the symptoms and has been attended by a recession of physical findings.

#### SUMMARY AND CONCLUSIONS

From an analysis of 100 cases of early filariasis the following conclusions appear justified:

1. The diagnosis of filariasis can be made in early cases prior to the appearance of microfilariae in the blood stream and prior to the formerly accepted physical findings.

2. The subjective symptoms are variable and may vary from area to area but the physical findings are quite constant for groups from all areas.
3. Certain evidence suggests that the symptoms and perhaps the physical findings of early filariasis are due to an allergic response of tissues sensitized to a circulating filarial antigen.
4. Experience thus far suggests that avoidance of reinfection will permit regression of symptoms and signs, and the probable eventual attainment of a completely asymptomatic state.

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## STUDIES OF FILARIASIS IN SOLDIERS EVACUATED FROM THE SOUTH PACIFIC \*

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IN recent months soldiers,<sup>1</sup> sailors and marines<sup>2, 3, 4, 5, 6</sup> have been evacuated to continental United States from various islands in the South Pacific Area because of suspected filariasis. The present report deals with our findings in 145 soldiers so evacuated, studied at Harmon General Hospital.

### OUTLINE OF STUDY

The patients studied had spent from two to 23 months (average 14 months) on tiny islands in the South Pacific on which filariasis due to *Wuchereria bancrofti* is endemic.<sup>7, 8</sup> The islands included Tongareva (Penryhn Island), Bora Bora, Aitutaki of the Cook Islands, Wallis Islands, Samoan group, Tongatabu, Woodlark Island, and the Ellice Islands.

The men had been evacuated from the endemic area within a few weeks of the time that the first symptoms appeared which were considered to be suggestive of filariasis. They arrived at Harmon General Hospital on the average in about two and one-half months after the onset of first symptoms. These facts must be kept in mind in any consideration of the probable future course and prognosis in these men. In contrast with the situation usually existing among natives exposed to repeated infections over years of time,<sup>9, 10</sup> these soldiers spent a comparatively short time in the endemic area under relatively good living conditions and were evacuated as quickly as practicable after the appearance of symptoms thought suggestive of filariasis.

The patients reached Harmon General Hospital in convoys over a period of about four and one-half months. Here they were studied and followed over an average period of about two and one-half months. In addition to the routine history, physical examination, and laboratory tests, special studies included: detailed history as to place and duration of oversea duty with reference to the earliest symptoms and the course of the disease; repeated examinations as regards lymphadenopathy, lymphangitis, and spermatic cord and scrotal abnormalities, made in cooperation with genito-urinary consultants; examinations of the stools for ova and parasites; repeated examination of the blood for microfilariae both by day and at night, with ordinary blood smears taken on at least seven days and examinations using the Knott concentration technic on at least three days; in certain patients microscopic

\* Presented in abstract form by Colonel Alexander Marble at the War Session of the American College of Physicians in Chicago, April 1, 1944.

examination of excised lymph nodes with a search for adult filariae; and in a few patients roentgenograms of the scrotum to detect calcified remains of parasites. Studies regarding intracutaneous and complement fixation tests will be presented later in the paper.

#### CLINICAL FINDINGS

It is impossible to present data of absolute accuracy regarding the onset, course and findings of the soldiers while in the endemic area. Many of the men were not hospitalized so that the medical records were incomplete. The summary of oversea findings as presented below is based on available medical records supplemented by the histories given by the soldiers themselves.

The acute symptoms at onset of the disease were those of lymphadenitis often with mild systemic manifestations such as malaise, nausea, vomiting, and pain in the lower abdomen. Swelling and tenderness of lymph nodes were noted usually in the inguinal region although often, axillary, cervical, and epitrochlear nodes were affected. Often present was unilateral scrotal involvement, especially on the left, with funiculitis, epididymitis, and swelling of the scrotal skin. Accompanying this there was in some cases a frank lymphangitis of retrograde type with development of the process away from the node. These manifestations of the acute stage lasted usually three to five days and in only a few cases were accompanied by significant fever or chills. The impression was gained from the soldiers included in our group that most of them were never very ill. The residual findings following acute episodes such as those described consisted of enlarged lymph nodes, induration along the lymphatic trunks with nodular thickenings, induration and tenderness of the spermatic cord, in some patients varicocele, and in rare instances hydrocele of a transient character.

Not all of the soldiers by any means had acute symptoms such as just described. In many of the men the presence of filariasis was not seriously considered until the time of a special physical examination made during a survey for possible cases. At this time the residual findings such as those just mentioned were noted in many of the soldiers; these heretofore had been regarded by the men themselves as due to various causes other than filariasis. On closer questioning some of them gave a history of having had three or four months before, a mild illness which may well have represented an acute phase of the disease. Once the symptoms and signs of filariasis were evident to medical attendants, soldiers were evacuated to the United States as soon as practicable. Included in the group evacuated to the United States were, no doubt, some who probably had no filarial infection whatsoever but in whom adenopathy and other findings, including a possible varicocele, were present before entrance into the endemic area or were acquired there from causes other than filariasis. The evacuation of such men was justifiable, however, so as not to expose to further infection any man who might have acquired the disease, even though in a mild form.

Upon arrival at Harmon General Hospital the men were, in general, in fairly good physical condition and had it not been for the necessity of observing them over a considerable period of time and the uncertainty with which their future was viewed, particularly at first, many of them could have gone to duty almost immediately. Physical examination revealed in almost

TABLE I  
Symptoms and Signs of 145 Patients with Suspected Filariasis

|                              | Lymphadenopathy |          | Lymphangitis |          | Scrotal edema |          | Funiculitis |          | Orchitis |          |
|------------------------------|-----------------|----------|--------------|----------|---------------|----------|-------------|----------|----------|----------|
|                              | No.             | Per Cent | No.          | Per Cent | No.           | Per Cent | No.         | Per Cent | No.      | Per Cent |
| During first attack overseas | 135             | 93       | 19           | 13       | 18            | 12       | 119         | 83       | 38       | 26       |
| At Harmon General Hospital   | 123             | 85       | 6            | 4        | 10            | 7        | 127         | 88       | 8        | 6        |

all of them enlargement of the inguinal, cervical, axillary and epitrochlear nodes. In many cases, however, it was difficult to decide just how much more than normal such lymphadenopathy was. Most of the lymph node enlargement was inguinal, more commonly on the left than the right side. Most frequent findings included thickening and tenderness of the spermatic cord especially on the left, varicocele especially on the left, and subcutaneous nodules or thickenings along previously involved lymphatic trunks. Following return to the United States and during a period of observation for two to six months at Harmon General Hospital, only six of the men had bouts of lymphangitis, which were uniformly mild. Of the six patients, two have had two attacks since return to this country. It is of interest that despite the predominant inguinal adenopathy, in every case but one the attacks of lymphangitis affected an upper, rather than a lower extremity. A given attack lasted from two to 10 days and as stated before, was accompanied by little or no fever, only one man developing a temperature as high as 101° F. Following a bout of lymphangitis the lymphatic trunk involved was frequently indurated with thickened, nodular formations throughout the affected course. In no case did elephantiasis occur either overseas or at Harmon General Hospital and in only a few instances was there even transient swelling of an extremity.

During the period of observation at Harmon General Hospital the tendency was definitely toward restoration to normal. The size of the lymph nodes tended to decrease, the tenderness and thickening of the spermatic cord tended to disappear and at the time of discharge from the hospital the condition of the men was almost invariably such as to allow them to pass a routine physical examination.

As part of the study the men were housed for at least two to four weeks

in convalescent barracks where graduated exercise was given leading up to five mile marches as a physical test prior to return to duty. In only three instances in whom attacks of lymphangitis were apparently precipitated, did exercise aggravate the condition. Furthermore, the attacks experienced by these three men were said by them to be not so severe as earlier episodes.

Examination of the blood for microfilariae was carried out with each patient on at least seven nights by the usual technic and three days by the Knott concentration method. This study revealed microfilariae in two instances and in these men the finding was made in each only once. In two other patients, microfilariae had been found in the blood overseas on one occasion each, in one man at a Station Hospital and in the second at Tripler General Hospital. Thus of 145 men, in only four were microfilariae found at any time and then on only one occasion in each patient. It should be pointed out that the disease observed in our patients was apparently of non-periodic type since this is the type of filariasis endemic in the area in which these soldiers served.

Routine laboratory studies in general yielded normal findings. The examination of the urine in almost all instances was normal. In keeping with the usual experience with the non-periodic type of filariasis, no case of chyluria was seen. No case of significant anemia was found, the white blood cell count in most patients was entirely normal and in no case significantly elevated, and the blood sedimentation rate was normal. In 47 patients the percentage of eosinophiles in the blood was 4 or greater at one time or another during the period of observation. The findings as regards eosinophilia in the 47 cases were in detail as follows: 4 per cent, 14 cases; 5 to 9 per cent, 24 cases; 10 to 14 per cent, three cases; 15 to 19 per cent, three cases; and 20 per cent and over, two cases.

In only four of these 47 were there significant findings in the routine stool examinations. Cysts of *Endamoeba coli* were found in two of these, each of whom had 7 per cent eosinophiles in the blood. Of the other two patients, one had *Trichuris trichiura* in the stools, with 10 per cent eosinophiles in the blood on one occasion and 17 per cent at another. In the stools of the second, ova of *Necator americanus* were found; this patient had 6 per cent eosinophiles in the blood. In the remaining 41 patients no cause for eosinophilia was found other than filariasis. This was true even in one patient in whom eosinophilia amounted to 18, 29, and 69 per cent in January, February and March (1944) respectively, and in a second in whom 35 per cent was found in December 1943 and 58 per cent in March 1944.

In 19 patients lymph nodes were excised and studied microscopically. Careful examination failed to reveal filariae or remains of filariae in the sinusoids or perivascular lymphatic channels. This experience is somewhat at variance with that of certain other observers<sup>1,4</sup> and may reflect a milder degree of infection in our cases. The lymph nodes in our patients were not normal, however, showing changes considered characteristic of a reactive lymph node. There was, in general, a lack of preservation of lymph follicle

structure with hyperplasia of lymphoid and to a lesser extent, of reticulum cells. Necrosis, calcification and eosinophiles were absent. The van Gieson stain showed occasional wisps of collagen indicating minimal fibrosis. A few of the sinusoids showed what appeared to be proliferation of endothelial cells, at times even filling the lumen of the involved lymphatic structure.

In 29 cases roentgenograms of the scrotum were taken in an attempt to demonstrate calcified remains of filariae but in only four cases were shadows seen. In each of three patients one small area of calcification about 2 to 4 mm. in diameter was seen; in the fourth there were three small areas ranging in size from 1 to 3 mm. in diameter. It must be pointed out that one can not be sure that in these four cases the calcification was an aftermath of filarial infection.

Simple, practical psychiatric measures formed an important part of treatment. As has been brought out by Rome and Fogel,<sup>2</sup> these men, having observed Polynesian natives with advanced stages of deforming elephantiasis, come to fear that later on, their own legs and their scrota will become conspicuously enlarged. Since the genital region is commonly affected, they worry that they will become sexually impotent, or sterile, or that they will infect their wives or future wives. To relieve this anxiety, repeated personal conversations and explanations and to some extent group discussions were employed, using all the encouragement and reassurance possible, consistent with the facts. Gradually, but very slowly, their fears were allayed.

The outlook for these men is uncertain but it is our belief that it is favorable. In the soldiers we have studied, the degree of infection has seemed mild and the clinical manifestations relatively few. One may have justifiable hope that since the men were brought out of the endemic area soon after the appearance of the first signs of the disease and, therefore, from then on kept free from reinfection, the disease will in time become entirely inactive as, in fact, it seemed to be well on the way to doing at the time of their discharge from the hospital.

#### INTRACUTANEOUS AND COMPLEMENT FIXATION TESTS

The clinical observations presented above were amplified by the carrying out of intracutaneous and complement fixation tests using antigens prepared from filariae obtained from animals. Such studies were considered important because of the relative paucity of information as regards these tests, particularly the complement fixation test, in filariasis and because of the variable results of the reports published by others.<sup>1, 2, 3, 11, 12, 13, 14, 15, 16</sup>

*Materials and Methods.* Antigen extracts were prepared at the National Institute of Health from the dog heartworm, *Dirofilaria immitis* and the horse filaria, *Setaria equina* by methods previously described.<sup>15</sup> Likewise prepared at the National Institute of Health were control antigens of dog and horse serum protein in dilutions corresponding to that of the filaria antigens.

In the intracutaneous tests, both direct and passive transfer technics were carried out in the usual manner. For direct tests, the outer aspect of the upper arm was used and intracutaneous blebs were made with the antigens and control materials (horse protein and dog protein in dilutions corresponding to the filaria antigens; 0.3 per cent phenol in physiologic solution of sodium chloride) in the different dilutions. A bleb about 6 mm. in diameter was formed by the injection of 0.05 c.c. of the test material. If in 20 minutes a wheal, associated with pseudopods and a zone of erythema, developed with a diameter which exceeded by at least 3 mm. that of the initial bleb (with allowance for the reaction produced by the control substance), the response was considered to be a positive immediate reaction. The test sites were reexamined for delayed reactions after 24 hours.

Passive transfer tests were made by the standard method of Prausnitz and Küstner, allowing a 48 hour interval before testing the sensitized sites in the recipients with dilutions similar to those used in the direct intracutaneous tests.

In both the direct and passive transfer tests, the reacting wheals were outlined with ink and transcribed on tracing paper on which measurements were made. The records were filed for future reference.

The complement fixation tests were carried out at the National Institute of Health, using a saline antigen prepared from *D. immitis* using the technic described elsewhere.<sup>15</sup>

*Results. Direct Intracutaneous Tests.* In table 2 are shown the results obtained in the direct intradermal tests. The 106 control subjects were physically fit soldiers who had never been outside continental United States.

TABLE II  
Results of Direct Intracutaneous Tests

| Subjects Tested                    | Total Cases | <i>D. immitis</i> —1:8000 |                 |                   | <i>S. equina</i> —1:8000 |                 |                   | Total Positive |          |
|------------------------------------|-------------|---------------------------|-----------------|-------------------|--------------------------|-----------------|-------------------|----------------|----------|
|                                    |             | Number Tested             | Number Positive | Per Cent Positive | Number Tested            | Number Positive | Per Cent Positive | No.            | Per Cent |
| Controls                           | 106         | 106                       | 4               | 4                 | 106                      | 5               | 5                 | 6              | 6        |
| Patients with suspected filariasis | 140         | 140                       | 65              | 46                | 139                      | 67              | 48                | 76             | 54       |

Among these there were four who gave a positive response to a 1:8000 dilution of *D. immitis* and five to a similar dilution of *S. equina*, or six in all who gave positive reactions to either or both of the antigens. Two others of the 106 subjects gave positive reactions to a 1:4000 dilution of *D. immitis*. The stools of the eight subjects mentioned were not available for examination for parasites or ova. Although on subsequent questioning all of the eight gave histories suggesting altered skin sensitivity as indicated by prevailing or recent attacks of dermatitis venenata, trichophyton infection, seborrheic

dermatitis or urticaria, no great importance can be attached to this information since it was not possible to question closely the remaining 98 control subjects.

Among the 145 patients with suspected filariasis, there were 140 who were tested with 1:8000 dilutions of *D. immitis* and *S. equina*. An additional seven patients (including two not in the total of 140 listed in table 1) gave positive reactions to a 1:4000 dilution of *D. immitis*; counting these, there were 83 or 58 per cent of 142 patients who gave positive tests.

*Passive Transfer Tests.* Passive transfer studies were carried out with the sera of 140 patients with suspected filariasis, using non-sensitive recipients as the test subjects. Positive results were obtained in 24, or 17 per cent, using *D. immitis* antigen, and in 35, or 25 per cent, using *S. equina* antigen, both in 1:8000 dilution. All told, there were 41 cases, or 29 per cent, in whom positive tests were obtained with either or both antigens in 1:8000 dilution. In two other cases, positive results followed the use of *D. immitis* antigen in 1:4000 dilution.

*Complement Fixation Studies.* Complement fixation tests carried out at the National Institute of Health gave positive results with the sera of 95, or 66 per cent, of 143 patients so studied. Since the experience with complement fixation tests in filariasis is relatively meager it was considered desirable to establish the degree of specificity of the test by a study of apparently normal individuals. In one series of 39 soldiers who had never been outside continental United States and whose home was in the northern half of the United States, positive complement fixation tests for filariasis were obtained in 10, or 25 per cent. These subjects were hospital patients who were convalescing from surgical, chiefly orthopedic, disorders of a nature as to make them "normal" for the purposes of the present study. In all cases examinations of the stools were carried out for ova and parasites and in only one patient were the tests positive; in this man on each of two examinations ova of *Necator americanus* were found.

As a second series of control subjects, 81 normal soldiers from Camp Fannin, Texas, were studied. Blood was drawn on the day of, and just following, the completion of a physical examination qualifying them for oversea service. All of the men were from the northern half of the United States and none had been in the Army more than four months. The following were the results of the complement fixation tests:

|                   |          |
|-------------------|----------|
| Negative          | 56       |
| Positive          | 13       |
| Doubtful          | 11       |
| Anticomplementary | 1        |
|                   | <hr/> 81 |

Of the 81 tests 13, or 16 per cent, were definitely positive. The high percentage of doubtful reactions was probably due to deterioration of certain of the sera incident to time required for transportation and storage. If one

excludes these from the series, thereby reducing the number to 70, then the 13 positive tests represent 19 per cent of the total. It is our belief that if the 11 samples had been suitable for testing, most of them would have been negative since over-long storage has a tendency to increase the binding power. Although the control data are unsatisfactory, the results indicate that the complement fixation test as carried out was positive in from 16 to 25 per cent of persons with no history of filariasis.

Thinking that perhaps the positive tests in these control groups were due to present or past trichina infestation, the sera of four of the men giving positive tests in the first group of 39 and eight of those giving positive tests in the second group of 81, were tested with trichina antigen. All were negative.

The anomalous results obtained in the case of these control individuals led to an investigation of the possible cause.\* In later antigen preparations, it was found that certain lots contained an unusual degree of opalescence apparently due to marked colloidal particulation. Titration of these antigens with the complement in overnight instead of the usual one hour fixation indicated marked anticomplementary properties. Since overnight titration for binding power was not conducted routinely with the tests reported above, it is probable that the positive results in some cases at least were due to a similar anticomplementary property of the antigens employed. No doubt further study will disclose additional factors responsible for the lack of specificity of the test in certain cases.

TABLE III  
Comparison of Results of Direct Intracutaneous and Complement Fixation Tests Using *D. immitis* Antigen

| Intracutaneous | Complement fixation |    |   |    |   |
|----------------|---------------------|----|---|----|---|
|                | +                   | +  | 0 | 0  | + |
| +              | 58                  |    |   |    |   |
| 0              |                     | 33 |   |    |   |
| +              |                     |    | 7 |    |   |
| 0              |                     |    |   | 42 |   |
| No test        |                     |    |   |    | 4 |

*Comparison of Results of Direct Intracutaneous and Complement Fixation Tests.* In table 3 are compared the results obtained in direct intracutaneous tests with *D. immitis* antigen (1:8000 dilution) and complement fixation tests using this antigen. It will be noted that there were 65 positive

\* Studies on the complement fixation test in filariasis are being carried out by Senior Zoologist John Bozicevich, Zoology Laboratory, National Institute of Health, who is responsible also for conducting the tests reported herein.

direct intracutaneous tests and 95 positive complement fixation tests. Of the total of 140 patients (excluding thereby the four patients who had complement fixation but no intracutaneous tests), in 100 or 71 per cent, there was agreement between the two tests, intracutaneous and complement fixation. In 33 instances, or 24 per cent, the complement fixation test was positive whereas the intracutaneous test was negative. In seven instances, or 5 per cent, the reverse was true.

In table 4 a similar comparison is made between the results of the complement fixation test and the direct intracutaneous test using a 1:8000 dilution of *S. equina*.

TABLE IV  
Comparison of Results of Direct Intracutaneous and Complement Fixation Tests Using *S. equina* Antigen

| Intracutaneous | Complement fixation |    |    |    |   |
|----------------|---------------------|----|----|----|---|
|                | +                   | +  | 0  | 0  | + |
| +              | 55                  |    |    |    |   |
| 0              |                     | 35 |    |    |   |
| +              |                     |    | 12 |    |   |
| 0              |                     |    |    | 37 |   |
| No test        |                     |    |    |    | 5 |

It is evident that there were 67 positive direct intracutaneous tests using *S. equina* in 1:8000 dilution. As stated before, there were 95 positive complement fixation tests. Of the total of 139 patients (excluding thereby five patients who had complement fixation but no intracutaneous tests), in 92 or 66 per cent, there was agreement between the two tests. In 35 instances, or 25 per cent, the complement fixation test was positive whereas the direct intracutaneous test was negative. In 12 instances, or 9 per cent, the reverse was true.

From the above it is evident that in 66 to 71 per cent of the cases there was agreement between the results of the complement fixation and the direct intracutaneous tests. This percentage, although not as high as might be desired, is nevertheless, great enough to indicate the possible value of the combined use of these two types of tests in the diagnosis of filariasis, particularly if the complement fixation test can be made more specific.

*Intracutaneous Tests with Other Filarial Antigens.* In addition to the intracutaneous tests carried out with high dilutions of *D. immitis* and *S. equina* antigen, direct and passive transfer tests were done in 75 of the patients with suspected filariasis using a 1:200 dilution of an antigen prepared from *Litomosoides carinii*, a filaria obtained from the cotton rat. This antigen was kindly supplied by Dr. H. M. Rose of the College of Physicians and Surgeons of Columbia University. Of the 75 patients tested, 58 or 77

per cent, gave positive reactions in direct tests. Of 50 patients tested, 23 or 46 per cent, gave positive reactions in passive transfer tests. Comparison of the results obtained in the direct intracutaneous tests and in the complement fixation tests shows agreement in 49 or 66 per cent of 74 patients with whom both tests were carried out. The use of a 1:200 dilution of *L. carinii* was not carried further because it is believed that in this relatively high concentration falsely positive tests are likely to be obtained. These falsely positive skin reactions due to sensitiveness to helminth and other related antigens may be avoided by the use of a filaria antigen in high dilutions such as 1:8000.

*Intracutaneous Tests with Antigens Other than Those of Filarial Origin.* Of 87 cases tested intracutaneously with both *Dirofilaria immitis* and *Trichinella spiralis* antigens, each in 1:8000 dilution, 48, or 55 per cent, gave positive immediate reactions to the former antigen but in only three cases, or 3.5 per cent, to the latter. In these three cases, positive reactions were obtained also with the *D. immitis* antigen. In these combined immediate reactions, the predominant reactions as measured by the diameter of the wheals were obtained with the filaria antigen. In 30 patients in whom passive transfer tests were done, positive wheal reactions were obtained in 21 per cent with *D. immitis* antigen in 1:8000 dilution with no positive wheal reactions when trichina antigen in like dilution was employed.

Forty-seven patients were tested with *L. carinii* antigen in 1:200 dilution and *Ascaris lumbricoides* extract in 1:100 dilution. The following results were obtained: In direct intracutaneous tests, 41, or 89 per cent, gave immediate positive wheal reactions with *L. carinii* antigen, whereas 20, or 42 per cent, gave immediate positive wheal reactions with ascaris extract. In passive transfer tests in 30 cases, eight, or 27 per cent, gave positive wheal reactions with *L. carinii* antigen whereas 5 or 17 per cent, gave positive immediate reactions with ascaris extract.

Because the clinical picture in filariasis was characterized by inguinal adenopathy and involvement of the scrotal structures in the majority of the filaria cases observed here, a differentiation from lymphogranuloma inguinale was desirable. In this connection the intracutaneous reaction is helpful. In 84 cases intradermal tests with Frei antigen (Lygranum) against a suitable control were made and read after a 24 and 72 hour interval. In these cases only two positive reactions were observed. In this same group of cases approximately 50 per cent gave positive reactions with *D. immitis* antigen in 1:8000 dilution and 89 per cent gave positive reactions with *L. carinii* in 1:200 dilution.

It is evident that in this group of patients the incidence of positive reactions to trichina antigen and to Frei antigen was low whereas that to ascaris extract was relatively high. However, in view of the recognized unreliability of intradermal tests with ascaris antigen, no great significance can be attached to the results obtained with this preparation particularly in the concentration used.

## DISCUSSION

The clinical findings presented in the first part of the paper are almost identical with those reported by others<sup>1,2</sup> who have observed American troops similarly affected. It is obvious that in our patients the infection was of mild degree. This may explain why in none of 19 cases studied were adult worms or remains of worms found on microscopic examination of excised lymph nodes. It is of interest that, despite this, microfilariae were demonstrated in the blood on one occasion in each of four patients (the positive smears were found at oversea hospitals in two of the patients).

Unfortunately, in persons so mildly infected as these men, it is difficult, using ordinary clinical and routine laboratory methods, to be sure of the diagnosis. It appears likely that most of our 145 patients with suspected filariasis actually were so affected. In only 13 cases or 9 per cent of the total, was clinical and laboratory evidence so scant that the diagnosis of filariasis seemed unwarranted. In an additional 10 or 15 per cent of patients the physical and routine laboratory findings were such that, although the diagnosis of filariasis was made, considerable doubt existed that the clinical features—lymphadenopathy, slight scrotal abnormalities and history suggesting a mild, acute phase of the disease some months before—really represented manifestations of filariasis.

Because of these considerations, particular interest was directed toward the results obtained with intracutaneous and complement fixation tests as aids in diagnosis. Although Taliaferro and Hoffman<sup>13</sup> in 1930 and Fairley<sup>11,12</sup> in 1931 and 1932 had carried out such tests, no great amount of work had been done along this line until recently when various workers<sup>1,2,4,7</sup> carried out studies on patients similar to ours. Most investigators have used extracts prepared from *Dirofilaria immitis* although Culbertson, Rose and Demarest<sup>14</sup> used an antigen derived from *Litomosoides carinii*.

Most workers have reported approximately 80 to 90 per cent positive direct intracutaneous tests in individuals with suspected filariasis using the antigens named above. However, the findings are open to criticism on two grounds: (a) Most investigators have paid insufficient attention to the strength of the antigen used for skin testing. Studies at the National Institute of Health have shown that when extracts as strong as 1:100 or 1:200 and indeed up to 1:4000 were used, falsely positive results are obtained due to group reactions in patients infected or formerly infected with other helminths. Many of these falsely positive reactions are avoided if dilutions of *D. immitis* antigen of 1:8000 are used. (b) With the status of the test as yet unsettled, an adequate series of normal controls should be tested by those studying cases of suspected filariasis. It is realized that this is impossible in oversea endemic areas, but studies carried out in non-endemic regions should include control subjects with no history of residence in an endemic area. Furthermore, both groups—filaria suspects and normal controls—should have examinations carried out for intestinal parasites. In

our own control series of 106 individuals, six gave positive skin reactions to either or both of two antigens, *D. immitis* and *S. equina* in 1:8000 dilution, and two others gave a positive response to a 1:4000 dilution of *D. immitis*. Wartman<sup>1</sup> states that 10.5 per cent of a control group gave positive reactions. (c) Adequate control tests should be carried out with antigens prepared from dog serum (horse serum if *S. equina* antigen is used) and other helminth (ascaris, trichina) antigens if available, in addition to the usual saline control substances.

Not many data are available in the literature regarding the outcome of complement fixation tests in filariasis. Lloyd and Chandra<sup>16</sup> found 23 positive tests in 89 patients with filariasis (26 per cent). Fairley<sup>11,12</sup> reported positive complement fixation results in individuals with filariasis as did Mohr and Lippelt.<sup>17</sup> The former used an antigen prepared from *D. immitis* and the latter investigators one prepared from *Contortospiculum rheae*. Bozicevich and Hutter<sup>15</sup> in the laboratory of the National Institute of Health obtained negative reactions in each of 25 patients from the United States Naval Hospital at Bethesda who had clinical evidence of filariasis with a history of exposure. Changes made later in the technic of the test<sup>18</sup> resulted in marked improvement in the sensitivity. Although in our series of patients with suspected filariasis positive reactions were obtained in 95, or 66 per cent, positive reactions were also obtained in a high percentage, 16 to 25 per cent, of control groups. It is obvious that much more work must be done with the complement fixation test particularly as to its specificity. Further studies both in individuals with undoubted filariasis and in carefully selected control figures are indicated. Unfortunately these studies are made difficult because in the preparation of the antigen, worms for extraction must be obtained from sacrificed dogs or horses; consequently the supply of antigen is apt to be limited and variable.

#### SUMMARY

1. Clinical findings and results of intracutaneous and complement fixation tests in 145 soldiers evacuated from the South Pacific Area because of suspected bancroftian filariasis, are presented.
2. Signs and symptoms suggestive of filariasis including lymphadenopathy, lymphangitis, scrotal edema, funiculitis, orchitis and varicocele, arose on the average after about 13 months' residence in an endemic area.
3. The symptoms were, in general, mild and only six patients experienced bouts of acute lymphangitis during the period of study in the United States. No case of elephantiasis occurred. No case of chyluria was encountered.
4. Microfilariae were demonstrated in the blood on one occasion in each of four patients (in two of these at oversea hospitals).
5. In 47 patients eosinophilia of 4 per cent or greater was found; in eight patients the percentage was 10 or greater.

6. Microscopic examination of excised lymph nodes in 19 cases showed only a non-specific inflammatory response ("reactive lymph node"). No adult worms or remains of worms were seen.

7. In four of 29 cases roentgenograms of the scrotum showed tiny areas of calcification. However, it is not possible to state that such calcification was due to the presence of *W. bancrofti*.

8. Direct intracutaneous tests using antigens of *Dirofilaria immitis* and *Setaria equina* in 1:8000 dilution gave positive responses in 54 per cent of cases as compared with 6 per cent in a series of 106 control subjects. Of 75 patients tested with a 1:200 dilution of *Litomosoides carinii*, 77 per cent gave positive reactions.

9. In passive transfer tests positive responses were obtained to either or both *D. immitis* or *S. equina* antigen in 1:8000 dilution in 29 per cent of cases. Of 50 patients tested with a 1:200 dilution of *L. carinii*, 46 per cent gave positive reactions.

10. Positive complement fixation tests were found in 95, or 66 per cent, of 143 patients studied. However, the complement fixation technic used can not be considered wholly specific since 16 to 25 per cent of normal control subjects gave positive tests. It is believed that improvements being effected in the technic of the test will reduce the number of non-specific reactions. There was agreement between the results of the complement fixation tests and the direct intracutaneous tests with *S. equina* and *D. immitis* in 66 and 71 per cent of patients, respectively.

11. No specific treatment was given. Therapy included a liberal diet, "reconditioning" by means of gradually increasing activity and psychotherapy to allay fears as to possible future complications of the disease. The outlook for the men is considered good because of the relatively short residence in the endemic area and the slight degree of infection.

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## THE UNUSUAL IN GASTROINTESTINAL ROENTGENOLOGY \*

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DURING the last 10 years there has been a marked increase in the number of qualified roentgenologists in this country.† The fact must be recognized that even with this group of specialists available, a large part of our population depends on internist, surgeon and general practitioner for diagnostic radiographic service. It is sincerely believed that the time will come and is not far distant when most cities of 20,000 population will support a qualified radiologist. In the meantime, where this service is not available or where the physician prefers to do his own diagnostic radiology, the greatest degree of skill possible must be attained.

It is with this thought in mind that a few cases of relatively rare gastrointestinal pathological processes are presented. Even the individual who spends all of his time in radiology is prone to ignore the fact that other pathological processes than cancer and ulcer may be visualized. It is an axiom that one does not diagnose the pathological process of which he is not aware or of which he does not think.

*Esophageal-Pharyngeal Diverticulum.* This is a true pulsion type of diverticulum, occurring on the posterior wall at the junction of the pharynx and esophagus. Due to anatomical muscular weakness in this area only slight resistance to pressure is offered. Once a small mucosal sac develops here, food particles collect and by their weight cause a gradual increase in size until a sac which may become huge forms between the esophagus and spine. Pressure forward may be so great as completely to occlude the esophagus. Barium solution in this sac is visualized on the fluoroscopic screen as a spherical or ovoid shadow at the level of the junction of the esophagus and pharynx. The esophagus, if the pressure is not so great as to occlude it completely, is seen to emerge from it high on its anterior surface.

### CASE REPORTS

*Case 1.* G. M., negro male, aged 55 (figure 1). This greatly emaciated negro man complained of vomiting and weight loss over a period of several months. On close questioning he admitted some difficulty in swallowing for five years. His main trouble, however, was vomiting after a meal without nausea. He attributed his trouble to pleurisy which he developed five weeks previously but which improved.

Physical examination revealed emaciation as the prominent finding. His voice had a hollow quality. No masses were palpated in the abdomen.

\* Received for publication March 13, 1945.

† In 1930 there were 1,005 radiologists in the United States. In 1940, 2,866 physicians stated that they were radiologists.—Information from American College of Radiology.

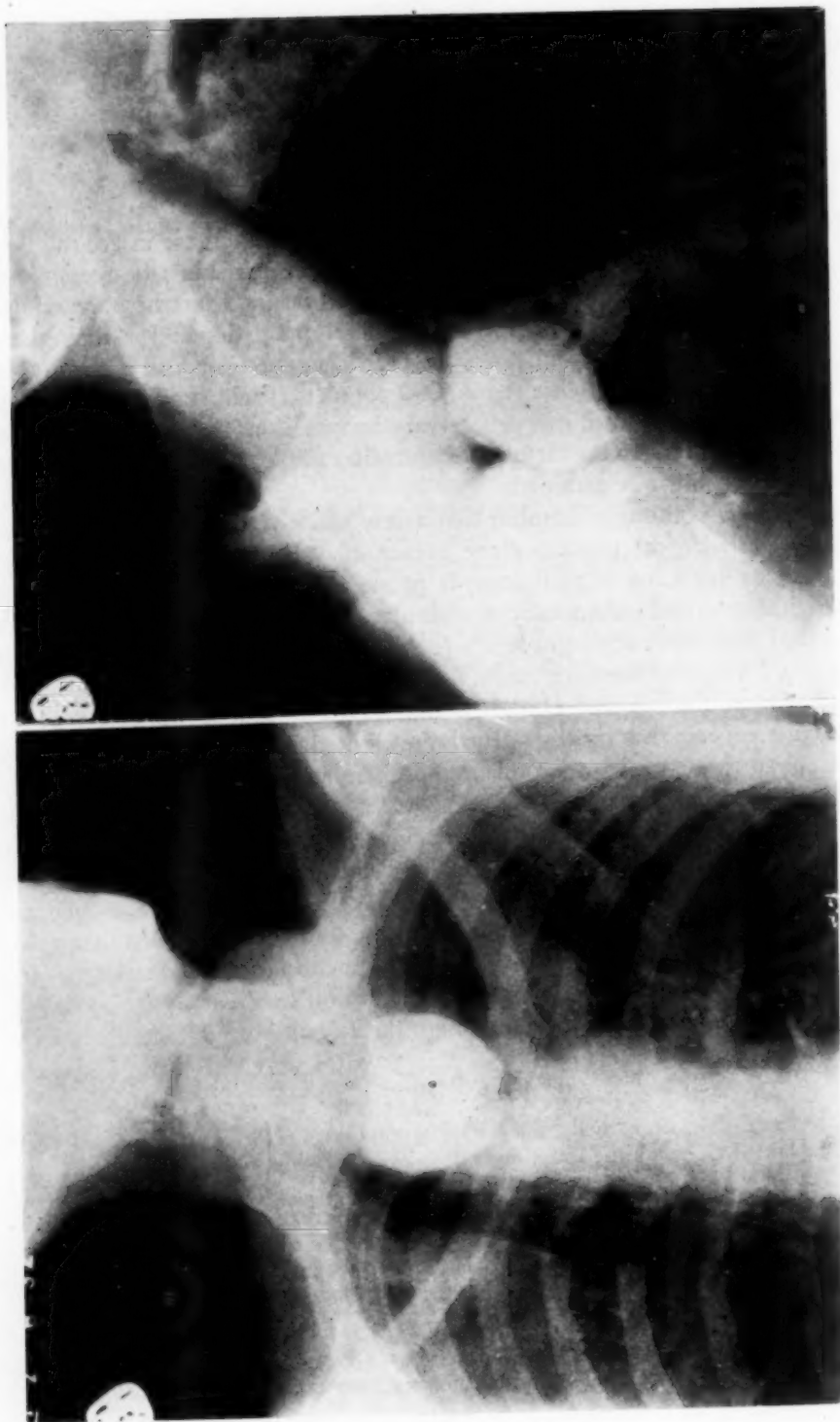


Fig. 1. Case 1. Esophageal-pharyngeal diverticulum.

Roentgenographic examination revealed a large esophageal-pharyngeal diverticulum out of which only a small quantity of barium solution spilled over into the esophagus.

Esophagoscopy was attempted but the opening into the esophagus could not be identified.

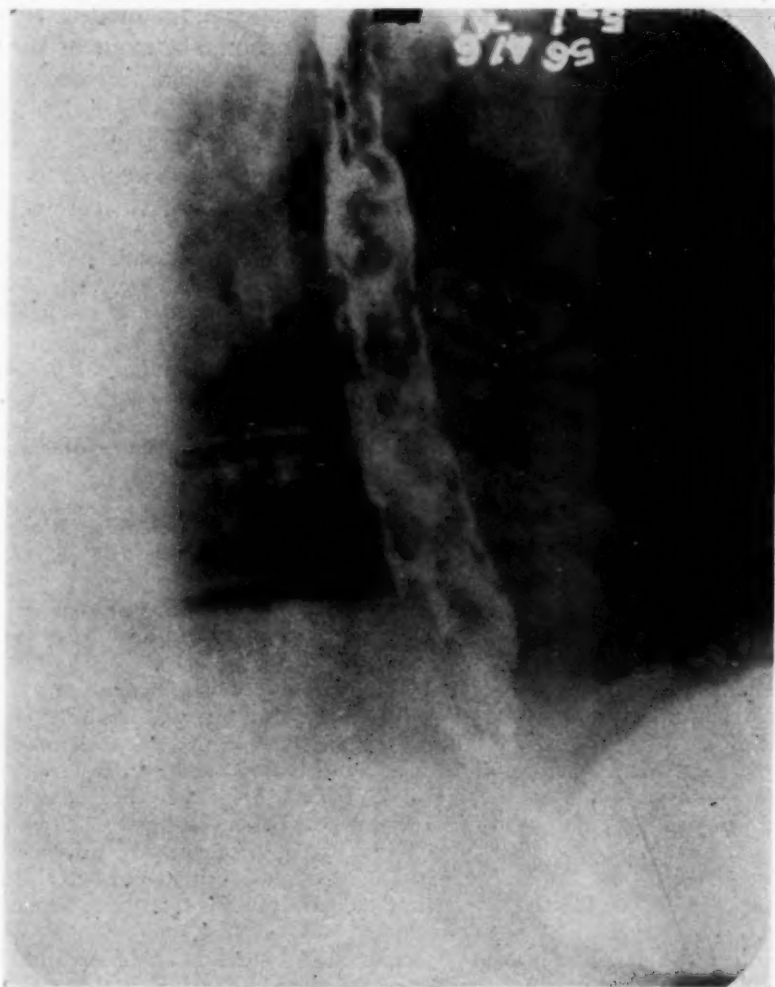


FIG. 2. Case 2. Esophageal varices.

Gastrostomy was performed but the patient was almost moribund at the time of operation and died a few days later.

At autopsy the following findings were recorded: "In the upper portion of the esophagus, just at the opening of the esophagus from the pharynx in the posterior wall is a diverticulum which measures  $7\frac{1}{2}$  by  $4\frac{1}{2}$  by 5 inches. This diverticulum lies on the posterior portion of the esophagus over which it hangs. In this way it folds over the opening to the remainder of the esophagus forming a slit-like aperture which under pressure is completely closed."

*Esophageal Varices and Gastric Varices.* These varices occur when it is necessary for the esophageal veins to form a collateral circulation. In any case of obscure bleeding from the gastrointestinal tract one should not omit a study of the esophagus and cardia of the stomach for varices. This process is usually not revealed by the routine study. The patient should be supine or in an oblique supine position. He should swallow moderately thick barium solution in a small quantity. Spot films should be made of the entire esophagus. The mucosal pattern will show as irregular trabeculation of negative shadows due to displacement of the barium by the varicose veins. There will be a beaded appearance where the veins are most numerous. Usually only the lower esophagus is involved although the entire esophagus and cardia of the stomach may show the typical pattern of varicose veins:

*Case 2.* H. H., white male, aged 35 (figure 2). The patient's chief complaint was weakness, vomiting of blood, and tarry stools. One week prior to admission into the hospital the patient became nauseated following a big meal and vomited several large blood clots. Vomiting occurred two more times this same day and there was bright red blood the last time. He became weak and faint following this episode. Stools the next day were black. There was no history of illness during the past, but the patient had noticed an enlargement of the abdomen for several years.

Physical examination revealed a mass in the upper left abdomen thought to be the spleen. Blood count was normal except for slight anemia.

Roentgenographic examination was reported as follows: "The esophagus shows a trabeculated pattern characterized by vermiform shadows due to negative filling defects in the barium filled esophagus. The picture is classically that of esophageal varices."

A diagnosis of Banti's disease was made and a large spleen was removed. This weighed 1,070 grams and was reported by the pathologist as showing chronic and acute splenitis.

The patient returned to the hospital four years later because of a profuse gastrointestinal hemorrhage. This was the first severe hemorrhage since the operation. Hemoglobin was 48 per cent. Roentgenographic examination showed moderate increase in the size of the varices. Treatment consisted of blood transfusions.

*Case 3.* L. S., white female, aged 48 (figure 3). The chief complaint was vomiting of blood and difficulty in swallowing. The patient had had a dull pain in her epigastrium for five years. Five days previously she became nauseated, vomited and passed tarry stools. She became weak and faint following this blood loss. On physical examination the spleen was not palpated and the liver was thought to be moderately enlarged.

Roentgenographic examination was reported as follows: "There is a proliferating lesion on the medial aspect of the cardia of the stomach that offers slight obstruction to passage of barium out of the esophagus. There is a tendency for rugae to converge towards this lesion. In a person of this age, malignancy is the diagnosis of choice. This lesion should be readily seen with the gastroscope." Gastroscoy was not done because of the fear of starting bleeding.

Operative note: "Cirrhosis of the liver, splenomegaly and varices of the stomach were found. Gall-stones were found and removed. An enlarged spleen was removed." The patient died of shock two days later. The spleen weighed 400 grams.

Autopsy notes: "Numerous varices were found in the cardia of the stomach some of which apparently have ruptured. A rather advanced periportal cirrhosis was found." No record of esophageal varices was found.

*Achalasia of the Esophagus.* This condition of achalasia of the esophagus is more commonly known as cardiospasm. Barium is not permitted to enter the stomach readily. The point of obstruction is at the cardia. If it is higher than this it must not be considered achalasia. The lower or cardiac end of the esophagus presents a smooth tapering conical contour as contrasted to the irregular contour of malignancy. Marked dilatation of the



FIG. 3. Case 3. Gastric varices.

esophagus is the rule with long standing achalasia. Apparent cardiospasm in an old person with but little dilatation must be looked on with considerable suspicion, as an early carcinoma may resemble or produce cardiospasm. Inhalation of the fumes of an amyl nitrite perle is a valuable means of making a differential diagnosis if in doubt. The spasm is usually relaxed in a few minutes if it is a spasm and not organic obstruction. In some cases the soft tissue shadow of the esophagus before barium is given will form a

shadow superimposed on the heart and mediastinum on the routine chest plate that will almost obliterate the detail of these structures.

*Case 4.* R. P., negro female, aged 42 (figure 4). The patient complained of nausea and vomiting and pain in the abdomen for a period of one year prior to admission.

Roentgenographic examination was reported as follows: "When the patient was first seen she had already been given two large glasses of barium solution. All of this was seen in a large viscus in the thoracic cage to the right of the midline. Sixteen hours following ingestion of this solution no barium had passed out of this viscus. The patient at this time was given a perle of amyl nitrite to inhale. Within a period of two minutes the solution emptied partly from the viscus above the diaphragm into the stomach proving that it had been retained in a dilated esophagus. Dilatation was due to achalasia of the esophagus and had undoubtedly been present for years to produce the dilatation seen."

*Hiatal Hernia.* Two types, the congenital and the acquired, are seen. The latter is much more common. In the congenital type there is a congenitally short esophagus that pulls a portion of the stomach through the hiatus of the diaphragm. In the acquired type a developmental widening of the hiatus occurs permitting sometimes a rather large sac to slip through to lie beside the esophagus. The hernia sac may be seen on the routine erect examination of the chest. It may or may not contain a small amount of fluid. It is best seen with the patient supine or sometimes prone. It is advisable to place the patient in the Trendelenburg position, after the barium meal has been given. The Valsalva maneuver is perhaps the most important step of all, carried out with the patient supine. The patient is directed to "Bear down as though you are going to move your bowels." If this is done, a hernia will often be visualized that was not suspected.

*Case 5.* C. M., white female, aged 60 (figure 5). The chief complaint was tiredness and shortness of breath. Fifteen years previously the patient had had an attack of precordial pain. She was told from electrocardiographic study that she had heart block. She has become progressively more incapacitated.

Electrocardiograph was reported as follows: "Levo rotation of the heart; prolonged A-V conduction consistent with an additional defect of nutrition. Abnormal rotation of the heart without further evidence of myocardial damage."

Roentgenographic examination: "There is a large developmental type of hiatal hernia."

Operative finding: "An opening was found in the diaphragm which could easily admit the tips of four fingers. This measured approximately 5 by 8 cm. in size. The opening was closed to a size that would accommodate the esophagus."

*Besoar.* The trichobezoar, a mass of hair in the stomach, may produce as in our case such a large mass that a cast of the stomach is formed. The phytobezoar usually produces a smaller mass. Persimmon seeds commonly form the nucleus for such a food ball. The dependable roentgen sign is a filling defect in the barium filled stomach which can be moved about. Peristalsis is not altered by the mass.

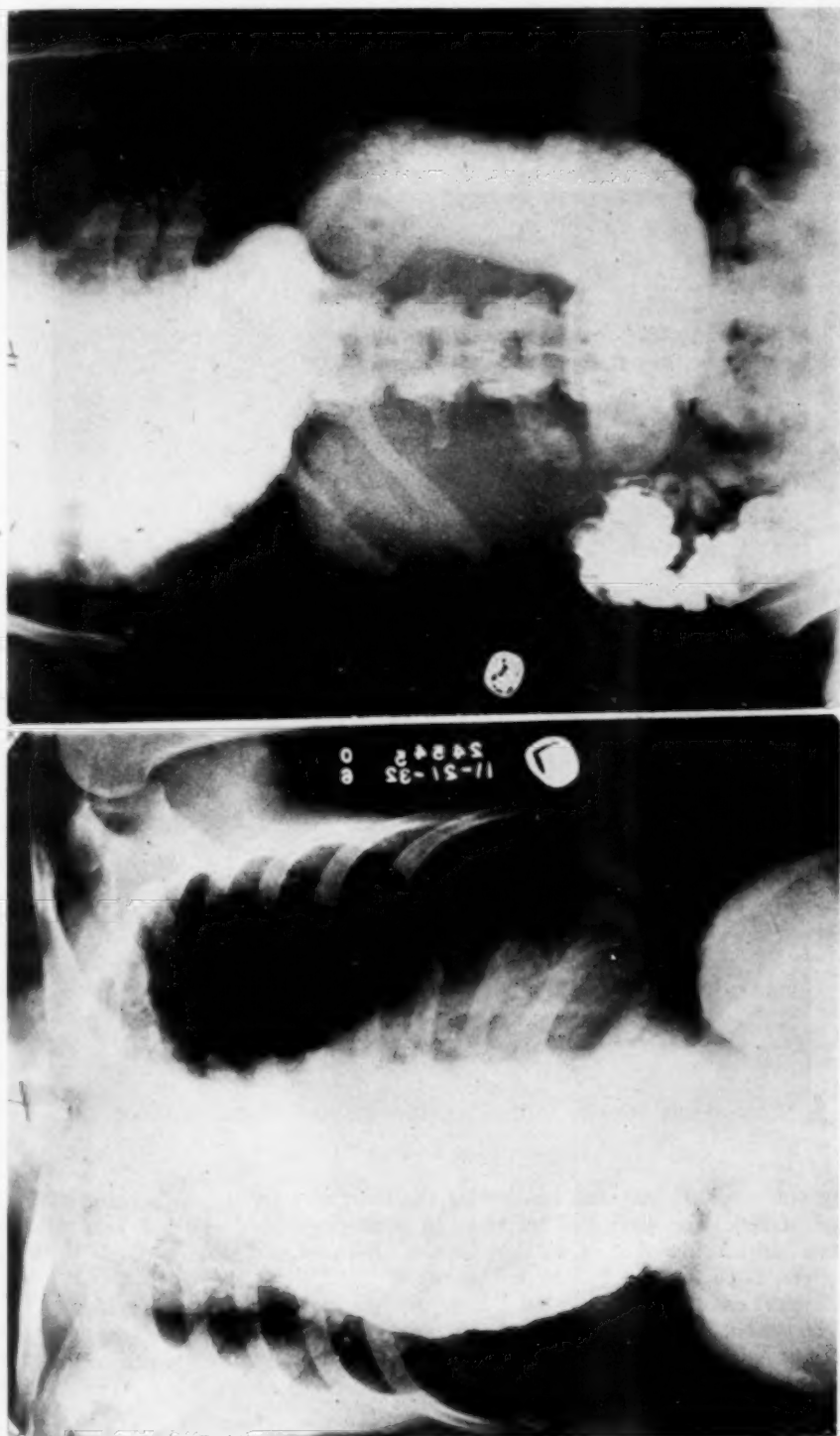


FIG. 4. Case 4. Achalasia of the esophagus.

*Case 6.* D. D., white female, aged 18 (figure 6). The patient complained of headaches, nausea and a mass in the abdomen. Six months prior to admission the patient was awakened one morning with a sudden sharp abdominal pain. This lasted two days and gradually disappeared. A small mass was found by the patient at this time. This mass has gradually increased in size. There was no other significant history obtained until after the operation. Then the patient's mother told of the child



FIG. 5. *Case 5.* Hiatal hernia.

pulling out wisps of hair and swallowing the hair, as a habit. This habit started at the age of six. The story had been told to other physicians who had been consulted but they had considered it of no significance. Because of fear of ridicule it had not been given as part of the history at this time.

Physical examination revealed a large midline mass that was not tender.

The patient was seen by several staff men and the following diagnoses were made by various individuals: (a) Tuberculous peritonitis; (b) enlarged spleen or liver; (c) malignancy of the stomach; (d) horse shoe kidney; (e) omental cyst; (f) retroperitoneal sarcoma.

Roentgenographic examination was reported as follows: "As the barium solution enters the stomach it appears to spread in all directions about a mass occupying the central portion of the stomach, causing the stomach contour to be clearly outlined with an area of central translucency. The barium visualizes a wide tube-like second and third portion of the duodenum. A constriction is seen in the barium column as it crosses behind the pylorus and another at the ligament of Treitz.

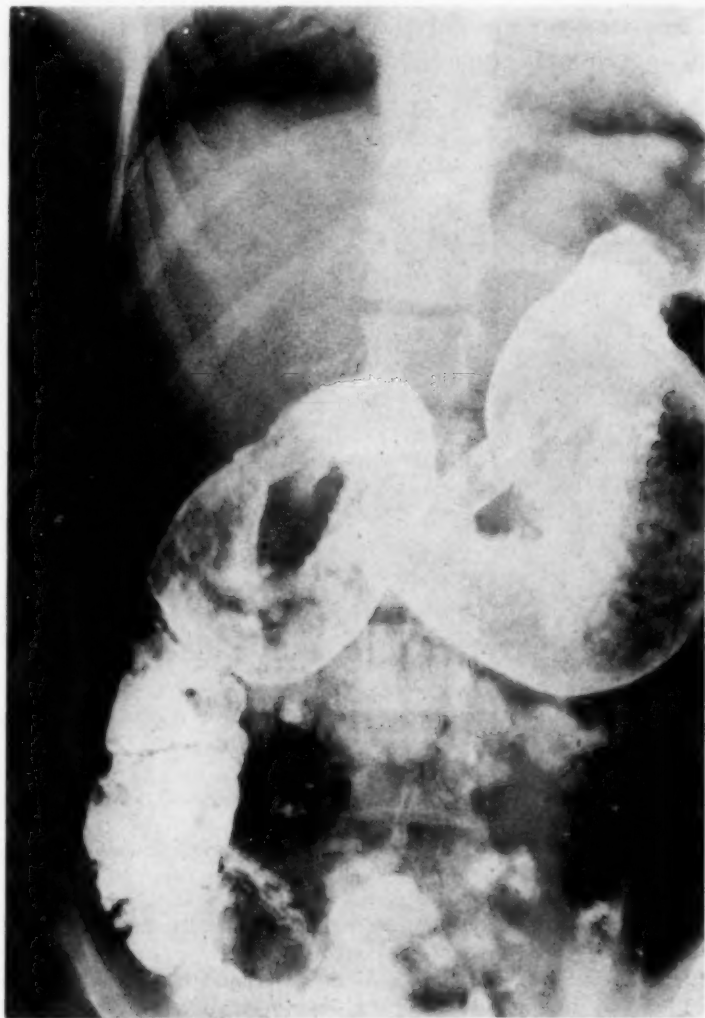


FIG. 6. Case 6. Trichobezoar.

At operation a mass of hair forming a cast of the stomach and duodenum was removed. The postoperative recovery was uneventful.

*Benign Tumors of the Small Intestine.* Tumors of the small intestine are very rare. Raiford<sup>1</sup> found in a series studied at Johns Hopkins Hospital 6.5 per cent of all tumors in the gastrointestinal tract arising from the

small intestine. Tumors of the carcinoid type were found to be infrequent. The "argentaffine tumors" or carcinoid tumors have their habitat chiefly in the cecum, terminal ileum, appendix, or sometimes in the ascending colon.<sup>2</sup> In the case described an important characteristic of the small intestinal tumor is demonstrated. This is the tendency of such a tumor to produce intussusception into the adjacent cecum. A large negative shadow is seen which resembles and may perhaps not be differentiated from a primary tumor of the cecum, as seen roentgenographically.

*Case 7.* L. T., white male, aged 50 (figure 7). The chief complaint was a lump in the lower abdomen and occasional colicky pain. The pain was first observed one month prior to admission, following a meal. Several similar attacks had occurred. There had been 15 pounds weight loss during the preceding two months.

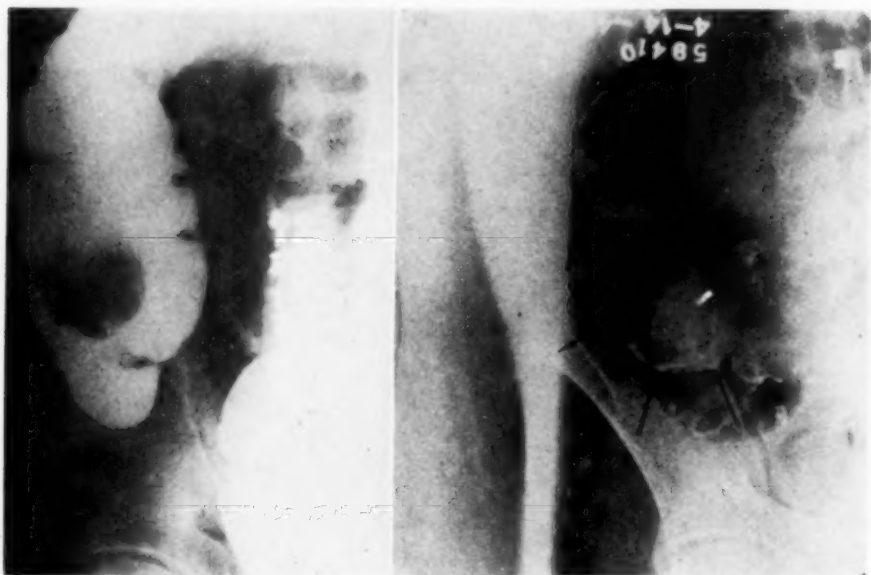


FIG. 7. *Case 7.* Intussusception of benign tumor of terminal ileum into cecum. Contrast enema and air instillation.

Physical examination revealed a semifluctuant tender mass in the lower right quadrant. This was about the size of a small lemon.

Roentgen examination visualized a filling defect in the cecum as it was filled with barium solution. A mass could be palpated here. Barium could not be forced through into the terminal ileum. It was thought to be a primary carcinoma of the cecum.

At operation the cecum was found enlarged owing to an intussusception. The intussusception was chiefly the last six inches of the terminal ileum invaginated into itself and into the cecum. After the invagination was freed a small tumor was found in the terminal ileum three inches from the ileocecal valve. Opposite the tumor in the mesentery were many enlarged glands. The wall of the ileum was thickened.

Pathological report was as follows: "Ulcerating argentaffine tumor or carcinoid of the terminal ileum with metastasis to the regional lymph nodes."

*Regional Ileitis.* Granulomata of the ileum were described in medical literature by Combe and Saunders in 1806.<sup>3</sup> During recent years many papers on the subject have appeared. The condition has been described under various names. Dalziel called it "hyperplastic enteritis"<sup>4</sup>; Crohn, Ginzburg and Oppenheimer referred to that type involving the terminal ileum



FIG. 8. Case 8. Regional ileitis. Double contrast enema.

as "regional ileitis."<sup>5</sup> Harris, Bell and Brunn described the process under the term "cicatrizing enteritis,"<sup>6</sup> and Carr and Boeck suggested the name "chronic ulcerative enteritis."<sup>7</sup>

Pathologically segments of the ileum, jejunum and even the colon may be involved. The segment of the gut involved in the process is thickened and edematous. The mucosa is ulcerated and in some cases hyperplastic.

Mesenteric glands are enlarged. Tubercle like structures may develop on the serosa. Later, cicatrization occurs.

The lesion may be detected with serial films of the small intestine after a barium meal. If the terminal ileum is involved it is best studied by a reflux of barium solution through the ileocecal valve into the terminal ileum. Early



FIG. 9. Case 9. Carcinoma of sigmoid. Double contrast enema.

in the disease the gut involved will show only slight narrowing of the channel, rigidity and possibly ulceration. Later the marked narrowing results in the "string sign."

*Case 8.* White female, aged 20 (figure 8). The patient complained of pain in the right side. This had been present for two years. One year prior to admission she developed painful subcutaneous nodules which were diagnosed erythema nodosum. These disappeared after one month. Recently she had developed weakness, nausea and pain in the side. The pain was cramp-like "as though something were trying to pass an obstruction."

Physical examination revealed a tubular non-tender mass just to the right of the umbilicus.

Roentgenographic examination revealed "a hyperplastic type of infiltration of the terminal ileum and cecum. The ileum throughout the terminal nine inches could be palpated as a tender, rope-like structure. The cecal head is also deformed." A diagnosis of regional ileitis was made.

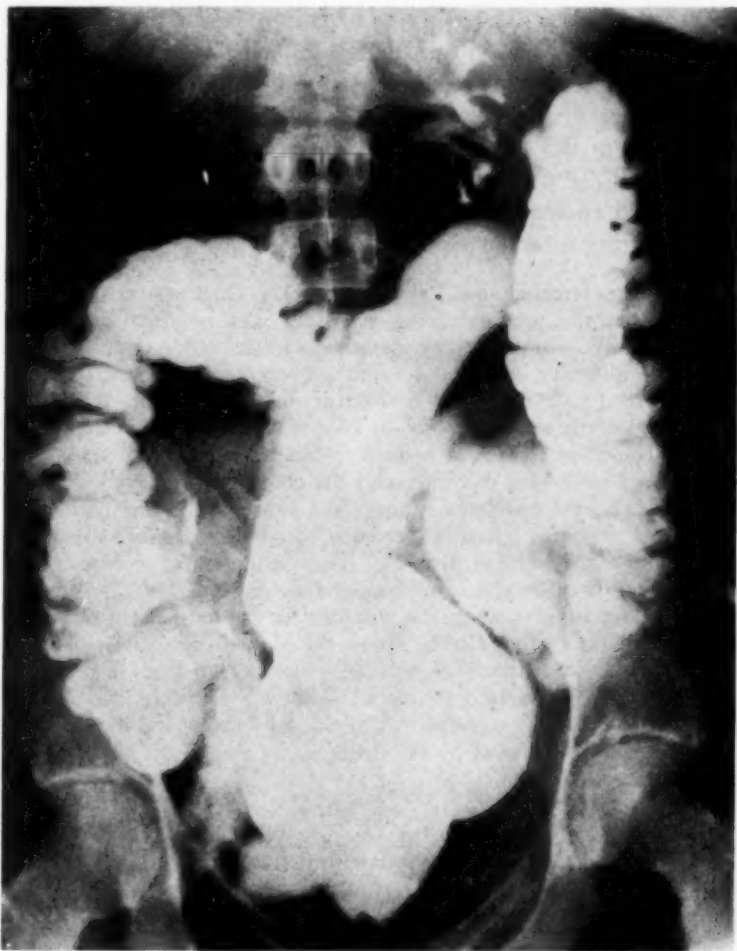


FIG. 10. Case 10. Ureteral-rectal fistula.

Operation: This consisted of removal of 35 cm. of terminal ileum, the cecum, and 15 cm. of ascending colon.

Pathology: "Chronic ulcerative granulomatous enteritis and cecitis; chronic granulomatous peritonitis, localized; chronic hyperplastic lymphadenitis."

The patient returned to the hospital two weeks after the first dismissal with a fecal fistula at the site of the previous operation. She had a diarrhea which soon became bloody. Roentgenographic examination showed a narrowed segment in the transverse colon and ulceration of the descending colon. Her condition became steadily worse. She died three months after the operation. There was no autopsy.

*Contrast and Double Contrast Enemas.* Examination of the colon is most satisfactorily accomplished with the contrast enema. Study of the colon with the barium meal is inconclusive and may be a dangerous procedure if there is obstruction. For visualization of the mucosal pattern, polyps and occasionally tumors the double contrast enema is valuable.

We wish to stress briefly the value of the double contrast enema in visualization of carcinoma of the colon. The colon is first carefully studied with the contrast enema. Following evacuation, with as little delay as possible, under fluoroscopic control enough air is instilled into the colon to fill it completely. Films are of more value than the fluoroscopic examination in making the final diagnosis. Often if the colon is redundant, the point of obstruction is visualized poorly because of superimposed overlying coils of gut. With the contrast enema this handicap is often overcome and the tumor will be seen invaginating into the air filled colon (figure 9).

*Case 9.* White female, aged 60 (figure 9). This patient had an occasional cramp-like pain but the predominating symptom was constipation. There was no blood in the stool. With the barium enema a point of obstruction was demonstrated with considerable difficulty because of a markedly redundant colon. No barium solution could be forced past the point of obstruction. A subsequent air injection not only demonstrated accurately the point of obstruction at the junction of the sigmoid and descending colon but showed it to be a medullary type of tumor.

At operation a medullary carcinoma of the colon was removed.

*Case 10.* M. S., colored female, aged 36 (figure 10). The patient's chief complaint was watery, frequent bowel movements. Five years before this the patient had had a hysterectomy for uterine fibroids. The postoperative course was uneventful except for a period of chills and fever lasting four days. The watery stools had been present for about three years when she was seen in the out-patient clinic.

Roentgenographic examination: "A normal colon is visualized. The kidney and ureter on the left are visualized as normal structures by the barium solution. The ureter can be seen to blend into the rectal shadow." A diagnosis of uretero-rectal fistula was made. This was subsequently verified by urological examination.

Surgical repair was refused by the patient.

#### CONCLUSION

The roentgenologist must have a sound background of pathology. It is not sufficient that he describe a pathological process. He must be able to express an idea as to the nature of the pathological process, the shadow of which is seen on his fluoroscopic screen or film. He will not be correct in every case but his opinion will gain respect as he develops skill and experience and above all as he develops a knowledge of the gross pathological possibilities.

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## ACUTE INFECTIOUS POLYNEURITIS (GUILLAIN-BARRÉ TYPE) \*

By JOSEPH G. CHUSID, Capt., MC, AUS, and GILBERT H. MARQUARDT, F.A.C.P., Lt. Col., MC, AUS, *Washington, D. C.*

ACUTE infectious polyneuritis is but one of the names of an entity called by others in the past polyneuritis with facial diplegia, acute febrile polyneuritis, motoneuronitis, acute infective neuritis, infective neuronitis, or meningomyeloradiculitis. The term Guillain-Barré syndrome has been used to designate those cases which clinically are characterized by an acute onset, mild or no febrile reaction, radicular neuritis, cranial nerve palsies, muscle tenderness, and which show certain cerebrospinal fluid changes.

The infectious nature of the agent causing this syndrome has not as yet been conclusively demonstrated. Attempts at culture and transmission to animals have been unsuccessful. Aring and Sabin<sup>1</sup> produced no effects in monkeys and mice inoculated with suspensions of tissue from the medulla and pons of a fatal case. The same investigators inoculated mice, guinea pigs, rabbits and rhesus monkeys with the pooled viscera (lungs, liver, spleen, adrenals and kidneys) from three fatal cases with negative results. Cultures of the same material were also non-productive. Honeyman<sup>2</sup> injected directly into the brains of rabbits saline suspensions of spinal cord, brain and peripheral nerves from three fatal cases without result. Despite the failure to transmit the disease or isolate a specific infectious agent, the apparent relationship of the disease to preceding infection in the body has frequently been noted. Upper respiratory tract infections have been especially associated with this entity.<sup>3,4</sup> Foster, Brown and Merritt,<sup>5</sup> in a review of 26 cases of polyneuritis with facial diplegia in a 10 year period at the Boston City Hospital noted that 50 per cent of their cases had a history of preceding upper respiratory infection. A review of seven cases of myeloradiculitis by Strauss and Rabiner<sup>6</sup> similarly emphasized the presence of preceding respiratory tract infection. Sabin and Aring<sup>7</sup> have stated that polyneuritis may be caused by a toxin elaborated by microorganisms of the upper respiratory tract. Garvey, Jones and Warren<sup>8</sup> in describing six cases observed in a two year period following hyperthermia treatments concluded that the disorder was a result of the activation of some infectious agent, perhaps a virus, by the fever. The case histories that follow show that clinically the gastrointestinal tract may be significant as a site of original infection.

Among the polyneuritides encountered in North America, acute infectious polyneuritis is reputedly second in frequency only to alcoholic poly-

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neuritis.<sup>9</sup> The association of this entity with military personnel in World War I was noted by Casamajor<sup>10</sup> and by Kennedy,<sup>11</sup> who described cases and autopsy reports among allied troops in France. The case reports following have all had their clinical beginnings in India, the first such to be reported to our knowledge. Three cases from North Africa, not included in the present report, have also been observed by us.

The pathologic studies by Honeyman<sup>2</sup> demonstrated little significant change in the nervous system. Kennedy<sup>11</sup> described a patchy neuritis in the peripheral nerves, degeneration of the cells of the anterior and posterior horns of the spinal cord and especially of the cells of the posterior ganglia, and small round cell infiltration around the ganglion and cornual cells. Casamajor<sup>10</sup> noted marked degeneration of the nerve fibers within the arachnoid space, most marked in the motor fibers, and increase of cellular neuroglia in the central gray matter, around the root fibers, and in posterior root ganglia. Aring and Sabin<sup>1</sup> noted scattered aggregations of lymphocytes and polymorphonuclear leukocytes in the interstitial tissue of the nerves of the cauda equina and comparable changes in the anterior and posterior roots. Roseman and Aring<sup>12</sup> noted in their three cases a marked degree of phagocytic reaction in peripheral nerves and its absence centrally. Gilpin, Moersch and Kernohan<sup>13</sup> described patchy degeneration of myelin and fragmentation of the axis cylinders of the peripheral nerves without evidence of inflammation. Jervis and Strassburger<sup>14</sup> reported a case in which there was degeneration of neuron cells, especially of the ventral horns, and breaking down of myelin sheaths with conspicuous glial reaction. The peripheral nerves showed some degenerative changes. Sabin and Aring<sup>7</sup> described changes in the adrenals, liver, heart, and kidneys consisting chiefly of focal infiltration with mononuclear cells and small areas of focal necrosis. Fitzgerald and Wood's case<sup>3</sup> showed a dense infiltration with lymphocytes and polymorphonuclear leukocytes in one large portal area.

The cerebrospinal fluid in patients with the Guillain-Barré syndrome is characterized by "albumino-cytologic dissociation"—an increased total protein with slight or no cellular response. During the progressive, earlier phases of the disease, the cerebrospinal fluid pressure may be considerably elevated. Ford and Walsh<sup>15</sup> reported a patient in whom decompression was done to save the patient's vision which was threatened by a progressive papilledema. The elevation of total protein in the spinal fluid may reach tremendous proportions. Bassoe<sup>16</sup> reported a total protein of 6,660 mg. per cent in a three and a half year old girl who subsequently recovered. The average range of values for total proteins, however, is considerably lower. Guillain<sup>17</sup> inferred that levels below 400 mg. per cent are indicative of abortive cases, but clinical experience generally in this country does not support that thesis. In many instances the determination of cerebrospinal fluid protein is not made at the height of the disease when the highest level is anticipated, because the importance diagnostically of this test is not recognized or because facilities are not available for its performance.

Mortality figures vary greatly. Guillain<sup>17</sup> predicated that all cases recover. Foster, Brown, and Merritt,<sup>5</sup> however, reported a 42 per cent mortality in their group, whereas Roseman and Aring's<sup>12</sup> review of 16 cases showed a mortality of 18.8 per cent.

This syndrome must be distinguished from other infectious diseases of the central nervous system as well as other types of polyneuritis. The chief entities to be differentiated are acute anterior poliomyelitis and diphtheritic polyneuritis. De Sanctis and Green<sup>18</sup> have elaborated on the problem of the differential diagnosis of acute anterior poliomyelitis and the Guillain-Barré syndrome. Progressive involvement, sensory changes, symmetrical ascending paralysis, and albumino-cytologic dissociation in the cerebrospinal fluid favor the diagnosis of the Guillain-Barré syndrome. Diphtheritic polyneuritis may be ruled out by the presence of a positive Schick test, the failure to find the pathogenic bacteria in nasopharyngeal smears and culture, and the absence of clinical signs and symptoms of diphtheria.

#### CASE REPORTS

*Case 1.* This 37 year old patient had been stationed in Karachi, India, when he noted on January 26, 1944 a "tired feeling" in both legs, numbness in the fingers and toes, and occipital headaches. During the next month the patient found it difficult to enter and leave his plane because of weakness in lower limbs; for a period of three days in mid-February he was aware of diplopia. On February 26, 1944 he was admitted to a Station Hospital where temperature, pulse, and respirations were found to be normal. Spinal fluid examination showed 1 white blood cell, 189 red blood cells, and Pandy slightly positive on March 6, 1944. Weakness in the lower limbs meanwhile became progressively worse; the patient now experienced difficulty in rising from a squatting position and could hardly walk forward or backward. By March 20, 1944, upon transfer to another station hospital, the patient required the aid of a cane in walking. On March 22, 1944 diplopia returned and persisted thereafter. Deep tendon reflexes were absent throughout; vibratory sensation was lost in both feet. Spinal fluid on March 22, 1944 showed initial pressure of 130 mm. of water, 1 white blood cell, positive Ross Jones test, colloidal gold 2210000000, and negative Kahn reaction. On April 23, 1944 the patient reached the Army Air Forces Regional Hospital No. 1, Coral Gables, Florida. At that time he could not stand unsupported and was quite tender over most of the muscles of the extremities. Deep tendon reflexes were absent throughout and vibratory sensation was absent from the level of the iliac crests downward. Mild diffuse weakness of the upper extremities with atrophy of most muscle groups of all extremities was present. On April 24, 1944 spinal fluid was under pressure of 235 mm. water, showed no white blood cells, a positive Pandy, total protein of 344 mg. per cent, and colloidal gold 35533420. The patient remained afebrile, complained bitterly of severe frontal headaches which on occasion were relieved by intramuscular injections of ergotamine tartrate. Despite repeated transfusions, supplemental feedings, high vitamin intake, parenteral infusions, the patient became progressively worse in that the level of severe muscle weakness continued to rise. On May 18, 1944 the patient was started on hot pack therapy to the extremities and back, but this was discontinued by May 29, 1944 because the tempo of progression appeared to hasten. By this time the patient was unable to rise or turn in bed and exhibited mild nuchal rigidity. Sense of position, vibratory sense, and stereognostic sense were lost in all extremities. The spinal fluid on May 27, 1944

showed an initial pressure of 275 mm. water, no white blood cells, 585 mg. per cent total protein, and colloidal gold curve of 1232334432. Spinal fluid was mildly xanthochromic at this time. Transfusions and intravenous infusions were now necessary to maintain adequate fluid intake. Lumbar puncture on June 14, 1944 showed a xanthochromic fluid under 210 mm. water pressure, no white blood cells, 732 mg. per cent total protein, and colloidal gold 3455554443. During the last week of June, the patient complained of recurrent transient episodes of difficulty in swallowing so that he refused all but small amounts of liquids by mouth. On July 19, 1944 the spinal fluid was intensely xanthochromic, showed 2 white blood cells per cu. mm., and total protein of 233 mg. per cent. Twelve hours later the patient went into acute respiratory failure; he suddenly became cold and cyanotic, and respirations were rapid, shallow and gasping. He complained of pain in the lower chest on both sides, but remained afebrile and had no cough. He was placed in an oxygen tent for several hours and then placed in a respirator. For the next eight days he remained in the respirator, being repeatedly transfused and receiving parenteral fluids. At the end of this time he was able to breathe satisfactorily again. Appetite improved thereafter and headaches decreased in frequency. In mid-August 1944 he began to complain of episodes of haziness of vision. Eye consultant noted two to three diopters of papilledema of both discs, with swollen veins and numerous scattered, large, flame-shaped hemorrhages. Symptomatically no great change occurred thereafter except for a transient episode of breathlessness, relieved by a 24 hour stay in an oxygen tent on September 11, 1944. The last spinal fluid examination was done on August 28, 1944, at which time the fluid was decidedly less xanthochromic than on previous occasions; initial pressure was 350 mm. water; there were no white blood cells, total protein was 815 mg. per cent, and colloidal gold was 0012212333. The patient was eating well and was able to sit up in a wheel chair.

*Case 2.* This 35 year old enlisted man was stationed in North Central India when, on February 28, 1944, he noticed a "fullness" in his abdomen and vomited. No chills, fever, diarrhea, muscular aches or other pains were present. On March 2, 1944 he developed a "sore throat." A week later he was admitted to a Station Hospital because of persistent headache, neckache, generalized muscle soreness, and regurgitation of fluids through his nose. On admission, oral temperature of 99.6° F. was noted; the uvula was found to deviate to the left; the right half of the pharynx, the soft palate, and the tongue were relatively insensitive to touch. Transient diplopia and vertigo were present on March 11. Complete blood count, urinalysis, blood smears for malaria, and nasopharyngeal smears for diphtheria were negative. On March 13 the patient was transferred to a General Hospital where the spinal fluid on the next day was found to contain 38 cells (95 per cent lymphocytes, 5 per cent endothelial cells) and a total protein of 83 mg. per cent. Colloidal gold and Kahn reaction on the cerebrospinal fluid were normal. Nasal speech, regurgitation of fluids through the nose, and absence of triceps, abdominal and left Achilles tendon reflexes were noted. Severe back pains were present on March 15; hot packs were applied three times daily to the chest, back, neck, and lower extremities for the following two weeks. By March 17 the low grade fever had returned to normal level. Repeat spinal fluid examination on April 8 showed 5 cells, total protein 125 mg. per cent, and a 2 globulin. Hypesthesia of the lateral surface of the right thigh, and return of the abdominal skin reflexes were now evident. Continued mild improvement persisted, but on May 16, 1944, at time of transfer to Army Air Forces Regional Hospital No. 1, he still showed moderate weight loss, slight dragging motion in the left lower extremity, small area of hypesthesia to touch and pinprick over right lateral thigh, absent Achilles reflexes bilaterally, and moderate difficulty in swallowing solid foods. Sedimentation rate, complete blood count, and urinalyses were normal. Swallowing function test on May 23, 1944 showed marked retention of barium in vallecula and

in each pyriform sinus, with coating of barium on pharyngeal walls after swallowing the barium. Under high vitamin, high caloric diet, the patient's swallowing function improved so that he was able to eat regular mess diet. He regained his lost weight and after convalescent training returned to duty on July 21, 1944.

*Case 3.* This 26 year old enlisted man had been in Calcutta, India for a month when, on April 13, 1944, he suddenly became ill with chills, fever, headache, backache, malaise, and pains in both legs and shoulders. He had been quite well previously except for a brief episode of diarrhea two months earlier. He noticed that his hand grasps were weaker than normal so that on this day he fell out of the cabin of a steam shovel he operated when he lost his grip on the levers. On April 13, 1944 he was admitted to a Station Hospital where the oral temperature on admission was recorded as 103° F. The patient complained of "tightness" in the muscles of all extremities at this time. The spinal fluid on the day of admission showed an initial pressure of 138 mm. water, 1 white blood cell, and was positive for globulin. (The total protein test could not be done.) Hot packs every two hours were applied to the extremities for a week. On the fourth day of packing, one of the safety pins holding the packs about the right leg was pinned through the skin for two hours without the patient's being aware of this. The temperature by this time had returned to normal. Examination on April 26, 1944 disclosed weakness of the right hand, right forearm, right leg, and right foot, with mild tenderness of the muscles of the right leg and arm. By June 10 the patient was able to work. On June, 28, 1944 he reached the Army Air Forces Regional Hospital No. 1 following evacuation from India, and examination here disclosed a mild limping gait favoring the right lower extremity, mild diffuse weakness of the right upper and lower extremities, and hypesthesia to touch and pain over the right upper and lower extremities. Complete blood count, urinalysis, blood serologic reactions and the sedimentation rate were within normal limits. On a program of physiotherapy, convalescent training, and high caloric, high vitamin diet, the patient became asymptomatic and returned to duty on July 16, 1944.

*Case 4.* This 21 year old enlisted man was assigned as a stable man in a cavalry company station in Northeast India. In February 1944, at least two mules he attended had mild "colds," and frequent sneezing and snorting. The mules recovered promptly; no other attendants were taken ill. On March 7, 1944 the patient began to regurgitate fluids through his nose, had sore throat and noted difficulty in swallowing foods. He reported to a frontier dispensary; an oral temperature of 102° F. was noted and the patient was hospitalized for 10 days. He received a course of sulfadiazine parenterally. For a four-day period while hospitalized he noticed diplopia. On discharge to duty he was still aware of mild difficulty in swallowing. Two weeks later, on March 30, 1944, he became aware of achy pains and numbness in both calves and feet, and stumbled frequently. Within another week, numbness and weakness were present in both arms and hands. He persistently avoided sick call and managed to remain on duty until May 10, 1944, at which time he was admitted to a Station Hospital. Temperature was normal at this time; repeated nasopharyngeal smears and cultures were negative for the diphtheria bacillus. Examination disclosed mild weakness of the soft palate, marked weakness of the lower extremities, absent Achilles and quadriceps reflexes bilaterally, and some loss of pain, touch, position and vibratory sensation in all extremities. The patient was given a course of sulfadiazine therapy, multiple vitamins orally, and physiotherapy, under which régime he improved mildly. He was evacuated to this country and reached the Army Air Forces Regional Hospital No. 1 on July 24, 1944. Examination here disclosed a limping gait, with the patient walking on his heels in attempt to protect his soles, which pained on weight bearing. Biceps, quadriceps and Achilles reflexes were absent bilaterally. Hypesthesia to touch and pain was noted in both lower extremities from the level of the knees downward. Sense of position was lost in both feet. There was moderate

motor weakness of the lower limbs affecting chiefly the glutei, hamstrings, quadriceps, extensors and flexors of both feet. Tenderness on squeezing was evident in both calves and over the anterior half of the right foot. Spinal fluid examination on July 30, 1944 showed an initial pressure of 160 mm. water, 4 white blood cells (lymphocytes), 79 mg. per cent total protein, positive Pandy, colloidal gold 004335420, and negative Wassermann reaction. Under a régime of intensive physiotherapy, high vitamin and high caloric diet, the patient showed moderate improvement in motor power, regained position sense in the feet, and was decidedly less tender in the calves and right foot.

*Case 5.* This 22 year old Second Lieutenant was stationed in Calcutta, India for two months prior to the onset of his illness. On March 18, 1944 he was suddenly seized with severe cramping pains in the abdomen and intense diarrhea. In the next three days he received sulfaguanidine as an outpatient at a dispensary with mild improvement in his diarrhea. On March 22 he noted severe frontal headache, orbital aching, low backache, and muscle pain in both lower limbs. He felt chilly during the night and the next morning, upon admission to a hospital, an oral temperature of 103° F. was noted. The patient's face was flushed, his abdomen was distended, and generalized hyporeflexia was noted. The spinal fluid was reported as being under "normal pressure," and contained 10 cells per cu. mm. By the next morning, flaccid paralysis of the lower extremities and abdomen was apparent. The spinal fluid showed "161 cells." (No other tests on the cerebrospinal fluid were done.) By March 25 numbness and tingling in the ring and little fingers of the left hand were present. Weakness of both shoulder girdle muscle groups and both arms was soon evident. Following transfer to a General Hospital, intensive hot pack therapy was instituted. Bladder catheterization every eighth hour was done until April 10, 1944, when normal bladder function returned. Moderate improvement in motor power of both shoulders occurred. Following evacuation to this country, the patient arrived at Army Air Forces Regional Hospital No. 1 on May 25, when examination disclosed severe flaccid paralysis from the level of the abdomen downwards. Mild power of dorsiflexion and plantar flexion persisted in both feet. The patient was unable to turn himself in bed or sit up. Both sciatic nerves were tender to palpation. A patch of hypesthesia to touch and pain was present over the left lateral thigh. The muscles of both lower extremities were moderately tender to palpation; simple touching of the skin of the lower extremities was uncomfortable. Spinal fluid examination the third day after admission disclosed no white blood cells, 83 mg. per cent total protein, positive Pandy, colloidal gold 1112222210, and negative Wassermann reaction. Nasopharyngeal culture for diphtheria bacillus was negative. Complete blood count and urinalysis were normal. Temperature, pulse and respirations remained normal throughout his stay. Continuous hot packs to the back, abdomen, and lower extremities were instituted on arrival. The patient showed mild improvement in motor power of both feet and had much less muscle tenderness and skin dysesthesia at the time of transfer to a General Hospital on August 1, 1944.

*Case 6.* This 24 year old pilot was stationed near Calcutta, India, when he was admitted to a Station Hospital on May 6, 1944 because of intense diarrhea, abdominal cramps, and fever of 101° F. He received symptomatic treatment with barium and paregoric, and because of finding of *Endamoeba histolytica* in the stool specimens, he received nine intramuscular injections of emetine hydrochloride and carbarsone by mouth. By May 25, he felt well enough to return to duty. On June 3, 1944 he first noticed numbness and feeling of "electricity" in both feet and legs. The next day, a similar sensation was present in both hands and forearms; he found writing difficult, for he could hardly hold a pencil in his hand. On June 6, 1944 he noted diplopia for the first time and was admitted to a Station Hospital. Temperature, pulse, and respirations were normal on admission. Examination revealed absence of deep tendon

reflexes, frequent stumbling on attempts to walk, hypesthesia to touch of both hands and feet. Intensive parenteral and oral vitamin B and multivitamin therapy did not alter the patient's status greatly by June 12, when he was transferred to another Station Hospital. On arrival here he complained of severe aching pains in both shoulders. Examination disclosed weakness in the grip of both hands, hypesthesia to touch and pain over both hands, partial paralysis of both external recti muscles, and winging of the right scapula. Spinal fluid examination on June 24, 1944 showed no white blood cells, positive Pandy (total protein could not be done), and negative Kahn reaction. Under physiotherapy and high vitamin therapy, weakness and hypesthesia of the hands receded. He was evacuated to this country and reached the Army Air Forces Regional Hospital No. 1 on August 2, 1944 where examination revealed marked winging of the right scapula, absent biceps, quadriceps and Achilles tendon reflexes, diplopia, and mild hypesthesia to touch and pain over the medial aspect of the left leg. Spinal fluid examination on August 10, 1944 revealed initial pressure of 160 mm. water, 7 lymphocytes per cu. mm., slightly positive Pandy, total protein 41 mg. per cent, colloidal gold 00011110000, and negative Wassermann reaction. The patient left the hospital on emergency furlough on August 14, 1944.

#### CONCLUSIONS

Six cases of acute infectious polyneuritis of the Guillain-Barré type with clinical onset in India are reported. Preceding gastrointestinal tract disease was noted in four cases and may be related to the onset of neurologic symptoms. The fact that many of these cases were primarily diagnosed as acute anterior poliomyelitis seems worthy of notation. The differentiation from acute anterior poliomyelitis can be made chiefly on the findings of albuminocytologic dissociation of the cerebrospinal fluid.

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## CASE REPORTS

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### ISOLATED (FIEDLER'S) MYOCARDITIS: REPORT OF CASE FIRST MANIFESTED BY ARTERIAL EMBOLI IN EX- TREMITIES AND TERMINALLY BY MURAL THROMBI IN THREE OF THE HEART CHAMBERS \*

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ACUTE isolated myocarditis was first described in 1900 by Fiedler.<sup>1</sup> It is a rare disease and one in which inflammation of the myocardium is apparently the only important acute lesion in the body. Engelhardt and Bruno,<sup>2</sup> in a recent review of the literature, collected nine cases from the American and 46 additional cases from the world literature. Various infections have been suspected as causing this disease such as acute upper respiratory infections, influenza, pneumonia, measles, virus infections, syphilis; also toxins have been suggested as etiologic agents circulating in the blood stream from diphtheria or streptococcus infections. Likewise implicated are vitamin B deficiency states, an allergic reaction or idiosyncrasy to bismuth, arsenic, sulfur, sulfonamides, alcohol, sparteine and adrenalin. Pregnancy, burns and hyperthyroidism have been associated respectively with certain cases. It seems safe to state at present that there is really no known cause, although recently Helwig and Schmidt<sup>3</sup> have described "a filter-passing agent producing myocarditis in anthropoid apes and small animals" obtained from hydrothorax fluid of a gibbon which dropped dead, and hydrothorax fluid and spleen of a chimpanzee dying very suddenly.

Grossly both animals had dilated hearts, pericardial effusion, pulmonary edema and bilateral hydrothorax and histologically pulmonary edema and an intense diffuse interstitial myocarditis "strikingly similar" to that in human acute interstitial myocarditis of unknown etiology.

The filter-passing agent was passed through a series of 122 mice, and with rare exception regularly produced paralysis followed by death or apparent recovery after a week or two. At necropsy interstitial myocarditis was found in almost all the animals. In some it was very severe; in others limited to small foci of necrosis and inflammation. The agent produces myocarditis in guinea pigs and rabbits, also. It is potent and specific when introduced intravenously, intraperitoneally, subcutaneously, intracranially, and by nasal instillations, and is present in the nasal washings of inoculated animals. It is destroyed by heating to 70° C. for 20 minutes, but withstands heating to 56° C. for 20 minutes, losing some of its potency, but not its specificity. It passes Berkefeld and Seitz filters. Such an agent has not been previously described, and strongly suggests that isolated myocarditis of humans may well also be a virus disease.

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Clinically, the most striking manifestations in humans are progressive myocardial weakness with dyspnea, precordial pain, tachycardia, cyanosis, low blood pressure and increase in the size of the heart. Most of the reported electrocardiograms have shown either prolonged PR or QRS intervals with inverted T-waves in one or more leads. Any combination of these abnormalities may be encountered. It occurs at any age, but is more frequent in young people. Some patients die suddenly; others have a protracted course extending for several months even up to two years. It is most frequently mistaken for coronary thrombosis, pericarditis or acute rheumatic myocarditis. The clinical diagnosis is made by exclusion. In a young person with a history of rapid, progressive myocardial insufficiency, the exclusion of the ordinary etiological factors, especially rheumatic fever, should lead one to consider acute isolated myocarditis as the clinical diagnosis.

Recently, we observed a case with this disease whose first symptoms were those of emboli to the left brachial and right popliteal arteries. These manifestations emphasize the observations previously described that the disease process may be present for a considerable time before symptoms appear. The patient's course was one of progressive myocardial insufficiency and death. At autopsy, there were large antemortem thrombi in three chambers of the heart. Microscopic examination of the myocardium revealed the characteristic lesions of this disease. Because of the rarity of the lesion and the unusual features of this case, we considered it worthwhile to add it to those previously reported.

#### CASE REPORT

The patient was a 25 year old, male Negro. There was no past history of rheumatic fever, chorea, diphtheria, scarlet fever, influenza, syphilis or hypertension. He had not taken any drug and had been eating an adequate diet. He was well until July 30, 1943. On that date, immediately after jumping out of a truck, he experienced sudden, severe pain and tenderness along the medial aspect of his left forearm with marked weakness of the corresponding hand. He was seen by a medical officer who described the left forearm and hand as "cool, pale with absent radial and ulnar pulsations." A diagnosis of thrombosis of the left subclavian artery was made. He was treated with rest, morphine, aminophyllin and warm wet dressings to the arm. The pain gradually subsided in two weeks and strength slowly returned to the arm, but the hand remained weak. Arterial pulsations continued to be absent. While still in the hospital, during convalescence, he awakened August 15, 1943 with a sharp pain in the right popliteal region. The pain extended rapidly to involve the whole right lower leg. The extremity became cold and arterial pulsations were absent. The severe pain subsided gradually over several days, but the leg continued to ache constantly and motor power in the right leg was very weak. During the latter part of August he had a severe attack of substernal pressure pain for eight hours. On September 16, 1943 there was a recurrence of substernal pain for several hours. The patient was admitted to this hospital on October 1, 1943. His complaints on admission were constant aching pain and weakness of the right lower leg and slight weakness of the left hand.

Upon physical examination, his blood pressure was 122 mm. Hg systolic and 86 mm. diastolic, temperature 98° F., pulse 84, and respirations 18. The heart was at the upper limits of normal size. No cardiac murmurs were heard. The left radial, ulnar, brachial and the right dorsalis pedis, anterior and posterior tibial and popliteal pulses were absent. Grip of the left hand was weak. There was weakness of the

right lower leg and it was cool to touch. An electrocardiogram (figure 1) showed rounded and inverted T-waves in all leads with a deep  $Q_{1 \text{ and } 2}$ .  $P_2$  and  $S_3$  measured 6 and 5 mm. respectively. The heart size was normal by chest roentgenogram (figure 2). There was a sedimentation rate of 30 mm. (Westergren method). The urine

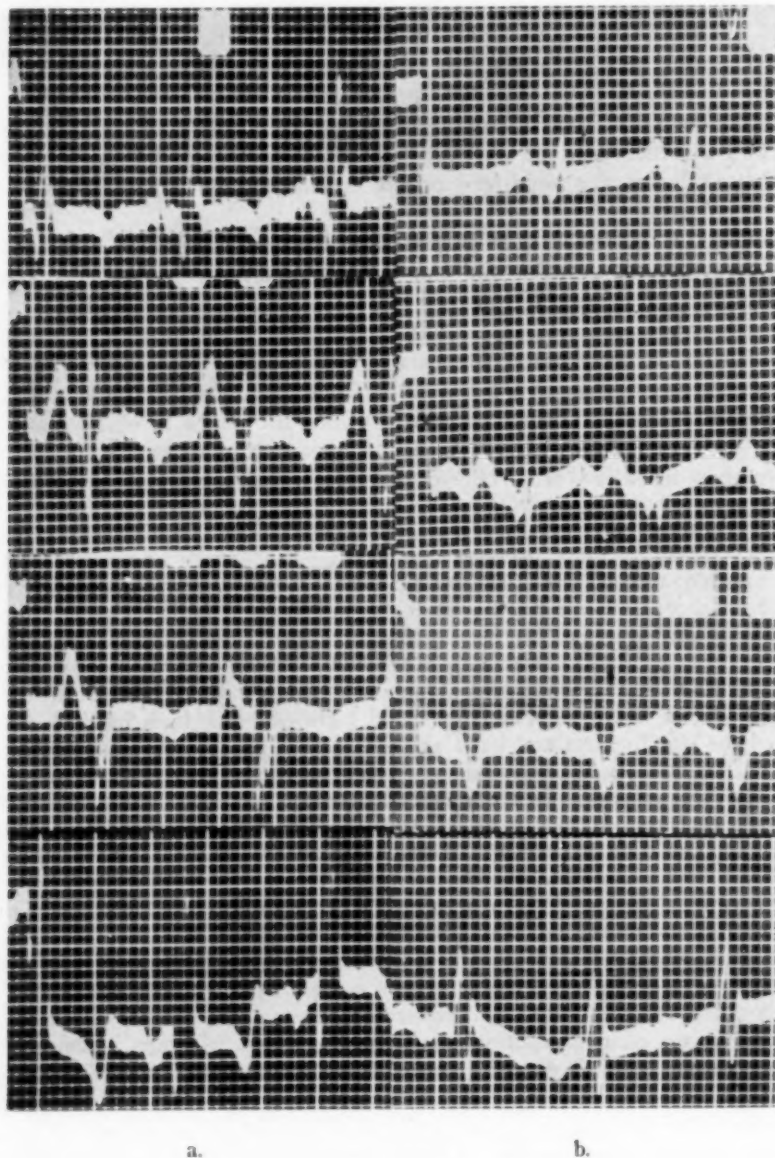


FIG. 1. a. Taken October 4, 1943, shows deep  $Q_{1, 2}$  with rounded and inverted T-waves in all leads. P-waves in Leads II and III are very prominent, indicating auricular hypertrophy. b. Taken December 4, 1943, shows a low electromotive force.  $Q_{1 \text{ and } 2}$  are still present.  $T_1$  and  $T_4$  are now diphasic.

was normal, the Kahn reaction negative, hematocrit 41 per cent, and the prothrombin time 22 seconds. A blood culture was negative.

The patient was treated with bed rest and aminophyllin 0.3 gm. t.i.d. He was given gradually increasing positive and negative Paevex treatments to the right lower leg from October 11 to November 15, 1943, until he received a positive pressure of 20 and a negative pressure of 80 for two hours daily. On this régime he had gradually decreasing pain and increased strength in the right leg. On October 26 he complained of mild dyspnea while in bed and a gallop rhythm was first audible at the apex. A right deep femoral phlebitis was evident on November 18 and on the same

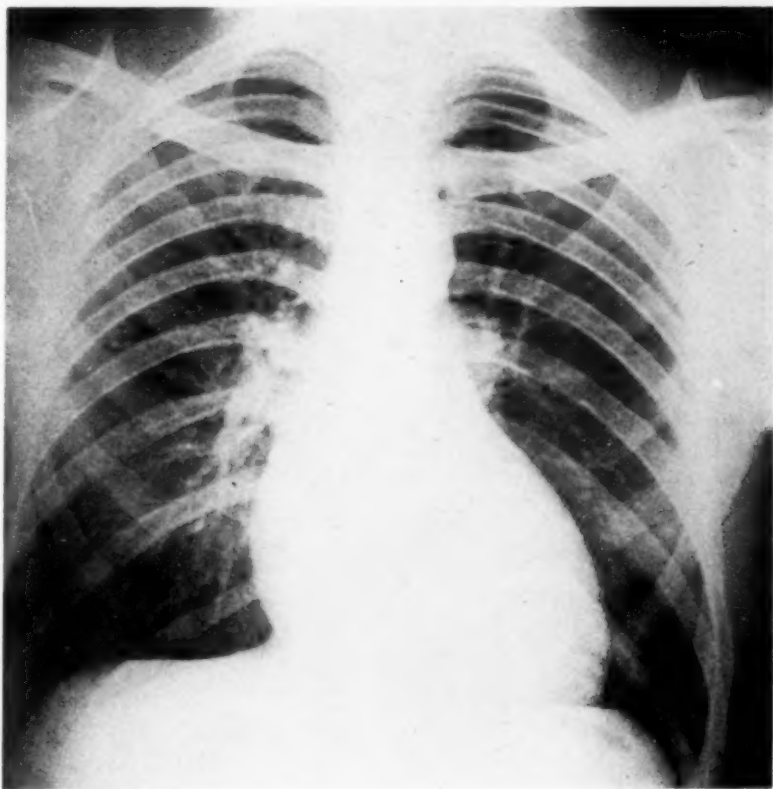


FIG. 2. Six foot chest roentgenogram taken October 4, 1943, shows the heart shadow at the upper limits of normal size.

day he had a pulmonary infarct with hemoptysis. The right femoral vein was immediately explored. The vein and surrounding tissues were acutely inflamed and the superficial femoral vein was completely occluded by an organized thrombus which extended upward into the common femoral vein and laterally into the profunda femoris. The clot was aspirated and the superficial femoral vein was ligated and cut. Following this episode the patient had fever from 99.6° to 102° F. daily until his death. He also complained of dyspnea at rest and the gallop rhythm became more prominent. Hemoptysis and physical signs of pulmonary infarction gradually subsided. On November 19, 1943 the patient noted severe right lower quadrant pain

with voluntary spasm and marked tenderness in the right lower quadrant. White blood cells numbered 18,100. It was thought that the patient probably had a right iliac phlebitis. However, because of the possibility of an acute appendicitis, an exploratory operation was done. A normal appendix was removed and the right iliac vein was explored, but no thrombus was palpable. The patient had relief of his right lower quadrant pain after this procedure. Another pulmonary infarction occurred on November 21, 1943, following which the heart became moderately enlarged and signs of heart failure, dyspnea, tachycardia, gallop rhythm and bifid apex impulse were evident. On December 4, 1943 the patient had an attack of severe substernal pain which lasted several hours. Following this, he became very drowsy and

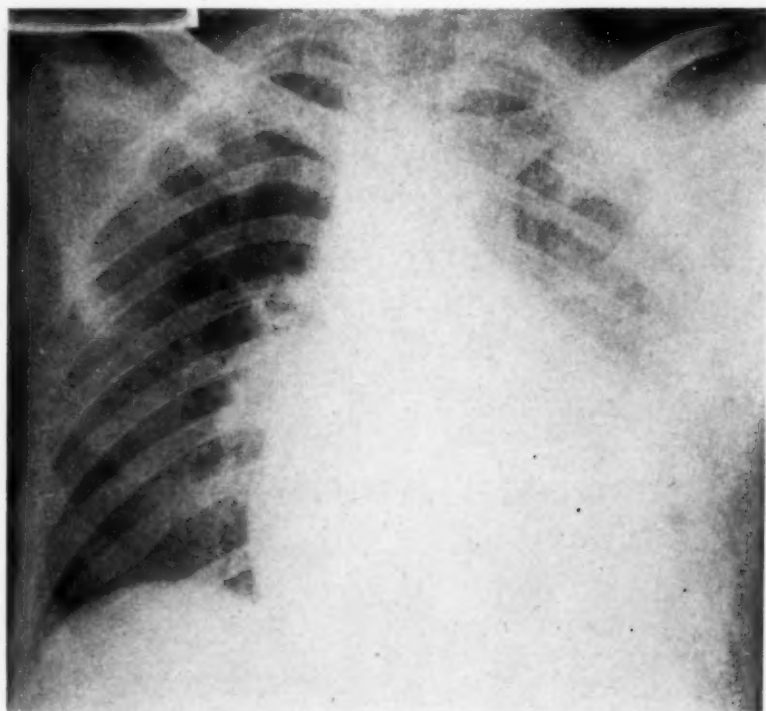


FIG. 3. Portable chest roentgenogram taken December 5, 1943, shows a marked increase in the cardiac shadow with the left border of the heart shadow extending to the left thoracic cage.

orthopneic. Moist râles were heard at both lung bases, the liver became palpable, and ankle edema appeared. The patient was rapidly digitalized without improvement. The signs of heart failure increased rapidly (figure 3). The blood non-protein nitrogen rose to 107. He died in his sleep on December 8, 1943.

**Autopsy Findings:** The external examination of the body was normal except for slight pitting edema of the right ankle. The heart weighed 610 gm. The epicardium was smooth and glistening. The chambers were all moderately dilated. Multiple rubbery, fairly firm, yellowish-red to dark bluish-red, firmly adherent thrombi were present in the right auricle, right ventricle and left ventricle (figures 4 and 5). The valve leaflets were smooth and delicate. The left ventricle varied in thickness

from 1.5 cm. to 0.7 cm. The right ventricle averaged 0.6 cm. The myocardium was of peculiar yellowish, beefy-red color, and firm. No areas of old or recent infarction were recognized grossly. The coronary arteries were widely patent and lined by smooth, glistening intima. The aorta measured 4 cm. in circumference at the level of the diaphragm, and was of normal elasticity. The intima was smooth except for an occasional small bright yellow atheromatous nodule. The inferior vena cava contained a large, bluish-red, free lying thrombus extending to 6 cm. above the bifur-

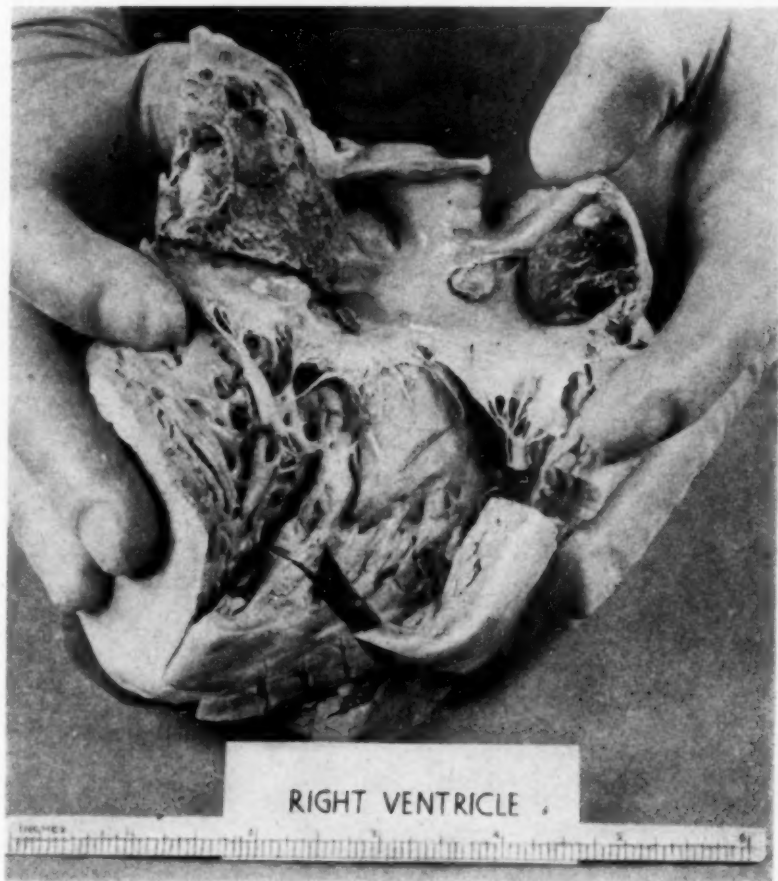


FIG. 4. Shows mural endocardial thrombi in right auricle and ventricle.

cation. It was firmly attached to the intima at the left of the bifurcation and it continued inferiorly with a large thrombus which completely occluded the lumina of the common iliac veins, extending distally in the left for a distance of 3 cm., and in the right throughout the right common iliac vein and femoral vein to the fossa ovalis, where the vein had been ligated by black silk sutures and a 2 cm. segment of the vein removed. The thrombus continued distally from the point of ligation down to the level of the mid-calf. After the body was embalmed the left brachial and the right femoral arteries and their branches were opened and examined to the wrist and ankle,

respectively. There was a small amount of material grossly resembling fibrin adherent to the wall of the brachial artery in its midportion (microscopic examination disclosed this as a completely organized thrombus and contracted residuum of a previous thrombus or embolus; see below): the right femoral system contained recent partially organizing clot. The posterior tibial artery was filled with a dark bluish-red thrombus.

The lungs were atelectatic in the lower portions, and contained small recent pulmonary infarcts. The small arteries leading to these contained adherent thrombi. Gross examinations of the intestinal tract, pancreas, spleen, liver, gall-bladder and adrenals were essentially negative. The kidneys contained multiple slightly depressed

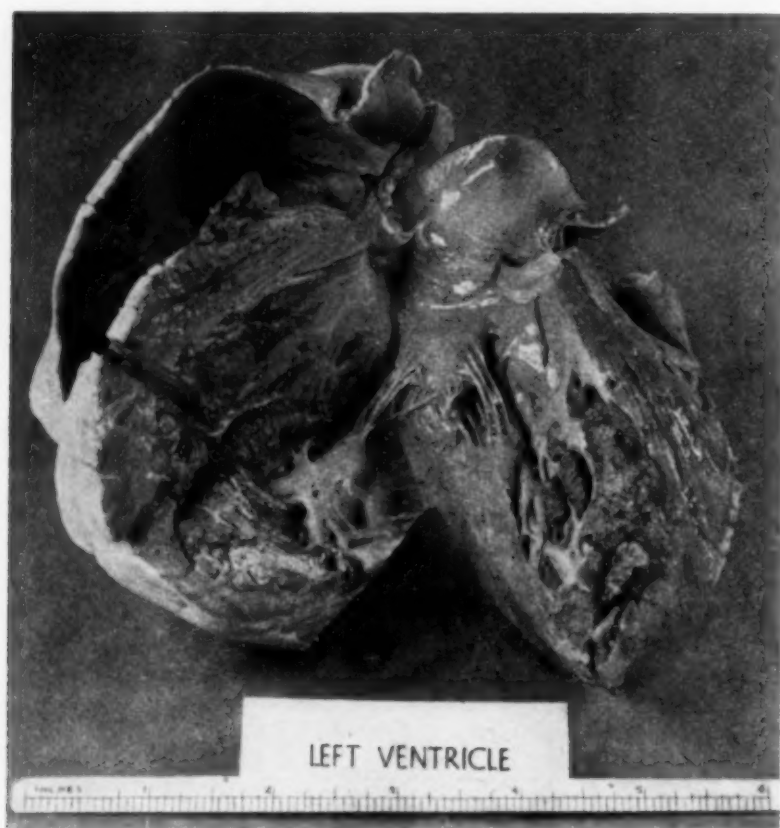


FIG. 5. Shows mural endocardial thrombi in the left ventricle.

infarcts in the lower pole of the left kidney and a small infarct in the midportion of the right kidney. The remainder of the genitourinary tract was grossly normal. The brain and spinal cord were normal. The muscular, osseous, lymphoid and endocrine systems were normal.

On microscopic examination the conspicuous pathological changes were found to be limited to the heart and vascular system. The myocardium exhibited extensive interstitial collagenous connective tissue deposition with occasional small foci of lymphocytes and other monocytes, together with a few plasma cells and scattered polymorphonuclear leukocytes (figure 6). The individual myocardial fibers show



FIG. 6. Interstitial fibrosis and cellular infiltration, with hypertrophy of cardiac muscle.  $\times 180$ .

marked, and often irregular hypertrophy, with extensive vacuolization in many fields. The mural thrombi showed partial organization immediately adjacent to the endocardium, primarily in the areas where the myocardial fibrosis had extended to the subendocardium. There were organizing thrombi in both iliac veins. The left ulnar artery contained several small completely organized polypoid thrombi which were firmly attached to the intima though these were contracted, and did not materially decrease the size of the lumen. The left brachial artery contained a similar completely organized thrombus. This, too, was contracted, so that it affected lumen volume little, if at all. The right posterior tibial artery contained a large laminated thrombus which was slightly organized at the periphery. Sections of the lung revealed multiple recent, old and organizing infarcts, and chronic passive congestion. Sections of the kidneys confirmed the gross impression of multiple ischemic infarcts with marked passive congestion, with adjacent arteries occluded by organizing thrombi. The reaction of repair and inflammation about these infarcts was surprisingly slight. Microscopic sections of the stomach, small intestines, spleen, pancreas, gall-bladder, adrenals, bladder, prostate, seminal vesicles, testes, endocrine glands, brain, bone, muscles, lymph nodes and breasts were essentially normal. The principal anatomic diagnoses were:

1. Myocardial fibrosis (Fiedler's myocarditis) with focal endocardial fibrosis.
2. Cardiac hypertrophy and dilatation.
3. Mural thrombi, multiple, partially organized, right auricle, right ventricle, and left ventricle.
4. Emboli, multiple, of left brachial artery (organized and recanalized, not occluding); of radial and ulnar arteries (organized and recanalized, not occluding); of right popliteal and posterior tibial artery (recent and partially organized); of small branches of the pulmonary artery (old, organizing and recent); and of renal arteries (partially organized).
5. Ligation and resection of 2 cm. of the right posterior femoral vein.
6. Thrombi (recent) of vena cava, common iliac veins, right popliteal, and right posterior tibial veins.
7. Pulmonary infarction, multiple (recent and old).
8. Renal infarcts, multiple, ischemic, bilateral, small.

#### SUMMARY

A case of isolated myocarditis of the Fiedler's type is presented. The first signs of the disease were emboli to the left brachial and right popliteal arteries. The course was one of progressive myocardial failure with chest pain, dyspnea, tachycardia, gallop rhythm and rapidly enlarging heart. The clinical diagnosis was myocardial infarction with mural endocardial thrombi resulting in peripheral emboli. Only after microscopic examination of the heart was the true nature of the condition established.

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## THE COMBINATION OF HYPERTHYROIDISM AND PERNICIOUS ANEMIA: REPORT OF A CASE WITH A REVIEW OF THE LITERATURE \*

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In the earlier literature on hyperthyroidism, anemia was regarded as one of the characteristic findings. From the reports, it is apparent that the diagnosis was usually made from the color of the face. Later on, when exact blood studies were performed, it was found that not only were the signs of anemia missing, but also that an increase in the number of red cells might actually be present in some instances. Kocher<sup>1</sup> was the first to stress this.

The relatively normal erythrocyte and hemoglobin values are emphasized by the data of several workers. In 678 cases of hyperthyroidism, Plummer<sup>2</sup> found an average of 4.79 million erythrocytes per cu. mm. with a hemoglobin of 83.1 per cent; Jackson<sup>3</sup> obtained an average of 4.79 million red cells and a hemoglobin of 78 per cent; and McCullagh and Dunlap<sup>4</sup> in 1200 cases noted an average of 4.55 million red cells with a hemoglobin of 82.5 per cent. In 20 cases reported by Wahlberg<sup>5</sup> the red cells ranged between 3.45 and 4.43 million (average 4.069) and the hemoglobin between 70 per cent and 80 per cent (average 75.5). The figures are somewhat higher in Deutsch's<sup>6</sup> cases: 3.3 to 5.5 million erythrocytes and 77 per cent to 102 per cent hemoglobin.

In fact some observers have noted an increase in the number of red blood cells. Zimmermann<sup>7</sup> examined 24 males and 76 females; in seven the erythrocyte count was below 4.0 million, in 27 it was above 5.0 million, in five above 5.5 million, and in one, more than 6.0 million. He noted no relationship between the blood count and the severity or duration of the disease. A very definite increase in red blood cells was reported by Schwanke,<sup>8</sup> who observed an erythrocyte count as high as 8.6 million. Blank<sup>9</sup> described poikilocytosis, sometimes combined with basophilic stippling, in 30 per cent of 17 patients with Graves' disease.

In some recent publications, the morphological blood picture in hyperthyroidism is often described as normal. Joll<sup>10</sup> states that the red cells are "seldom much altered," and that only in advanced cases does one find poikilocytosis, polychromatophilia, and basophilic stippling. Means<sup>11</sup> says there is no characteristic change, as do Lawrence and Rowe.<sup>12</sup> According to Crotti,<sup>13</sup> Fleischhans,<sup>14</sup> and Kleiner and Renyi-Vamos,<sup>15</sup> the blood picture exhibits deviations from the normal only in severe cases, when the findings are those of a secondary anemia. Our own findings in a series of cases of hyperthyroidism and hypothyroidism (table 1) reveal no striking or characteristic changes in the blood pattern.

Although the theory has been advanced that the thyroid stimulates hematopoiesis,<sup>16</sup> the combination of polycythemia and hyperthyroidism is infrequent. A search of the literature reveals that only nine cases have been reported<sup>17, 18, 19, 20, 21, 22, 23</sup>; the diagnoses in five of these are questionable. We have observed this combination on one occasion.

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TABLE I  
Correlation of Data in 20 Patients with Hyperthyroidism and 25 with Hypothyroidism<sup>1</sup>

|                                   | Hyperfunction |                   | Hypofunction |         |
|-----------------------------------|---------------|-------------------|--------------|---------|
|                                   | Range         | Average           | Range        | Average |
| Age (years)                       | 21-50         | 36.2              | 14-65        | 34.2    |
| B.M.R. (%)                        | +10-+72       | 31.2 <sup>2</sup> | -4--22       | -13.23  |
| Hemoglobin (%)                    | 54-115        | 78.7              | 60-100       | 79.7    |
| No. of red cells<br>(per cu. mm.) | 3.45-6.5      | 4.274             | 3.5-5.2      | 4.387   |
| Color index                       | 0.65-1.15     | 0.944             | 0.9-1.1      | 0.96    |

<sup>1</sup> Two cases of hyperthyroidism are not included in this summary. The one case was probably connected with a pernicious anemia. However, a thorough study could not be made. The other patient suffered from a polycythemia.

<sup>2</sup> Not including two cases with b.m.r. of +4.2 and +4.0, respectively (after operation).

A profound anemia, even pernicious anemia, is more likely to be seen in combination with frank myxedema than with hyperthyroidism. As Means, Castle, and Lerman<sup>24</sup> remark, "That pernicious anemia may resemble myxedema, and that myxedema may resemble pernicious anemia, has long been apparent."

In view of the above, the coexistence of hyperthyroidism and pernicious anemia is quite remarkable. Handbooks on endocrinology and hematology either do not mention the combination at all, or only to say that they have not observed it. Youmans,<sup>25</sup> for example, writes that "in parts of the country where both diseases occur frequently, their combination is not seen."

On the other hand, 28 authors have reported this combination in 75 instances (table 2). In some of these cases, however, the diagnosis of pernicious anemia seems not to have been fully established, e.g., Schaumann and Saltzmann<sup>26</sup> question the diagnosis in Kerppola's cases.<sup>27</sup> Some reports of the combination may have escaped our notice because of the title under which published, whereas a number of others undoubtedly have never been reported at all. Apparently Suzman<sup>28</sup> saw the two conditions together; for, on reporting the basal metabolism in pernicious anemia, he states that cases with a thyroid condition are not included. Davidson and Gulland<sup>29</sup> mentioned patients with pernicious anemia following exophthalmic goiter, but gave no details. Meulengracht<sup>30</sup> claimed his attention had not been drawn to this problem in the beginning of his study. The same conclusion can be drawn from Stenstam's publication.<sup>31</sup> In his records, both diseases occurred together three times in a series of 192 cases of pernicious anemia observed between 1929 and 1938; but among the cases admitted to the hospital in 1938 alone, he found the coincidence four times.

Of the 75 cases listed in table 2, a total of 50 was reported by six authors,<sup>30, 31, 32, 33, 34, 35</sup> and the remainder by 22 examiners.

The occurrence of other diseases in the course of pernicious anemia is not infrequent. One hundred eight (17.2 per cent) of Giffin and Bowler's<sup>33</sup> 628 patients with pernicious anemia suffered also from other diseases. Wilkinson<sup>34</sup> saw concomitant maladies in 98 (26.4 per cent) of 370 patients. Of these, endocrine disorders were the third most frequent; and of the endocrine patients five had exophthalmic goiter, one hyperthyroidism, and three myxedema.

TABLE II

Data in All Reported Cases of the Combination of Hyperthyroidism and Pernicious Anemia

| Author                                     | No. instances of combination of P.A. & H. | Sex | Age  | Total No. Cases |      | Order of Onset |          |         |
|--|---|-----|------|-----------------|------|----------------|----------|---------|
|  |   |     |      | P.A.            | H.   | P.A. first     | H. first | Simult. |
| Adler <sup>71</sup>                        | 2   | f   | 51   |                 |      |                | +        |         |
| Aitoff and Loewy <sup>72</sup>             | 1   | f   | 44   |                 |      |                | +        |         |
| Andrus and Wintrobe <sup>23</sup>          | 5   | m   | 54   | 430             | 1180 | +              |          |         |
|  |   | f   | 31   |                 |      | +              |          |         |
|  |   | f   | 43   |                 |      | +              |          |         |
|  |   | f   | 47   |                 |      | +              |          |         |
|  |   | f   | 61   |                 |      |                |          | +       |
| Bauer <sup>73</sup>                        | 1   | f   | 49   |                 |      |                | +        |         |
| Billings <sup>80</sup>                     | 1   | f   | 36   | 20              |      |                |          | +       |
| Burwell, Smith and Neighbors <sup>23</sup> | 1   | m   | 23   |                 |      |                | +        |         |
| Faber <sup>81</sup>                        | 1   |     |      |                 |      |                | +        |         |
| Fernandez <sup>82</sup>                    | 1   | m   | 15   |                 |      |                |          | +       |
| Fleischhans <sup>14</sup>                  | 1   |     |      |                 |      | +              |          |         |
| Giffin and Bowler <sup>23</sup>            | 5   |     |      | 628             |      |                |          |         |
| Gulland and Goodall <sup>72</sup>          | 2   | f   | 25   |                 |      |                | +        |         |
|  |   | f   | 45   |                 |      |                | +        |         |
| Hansen <sup>77</sup>                       | 1   | f   | 30   |                 |      |                | +        |         |
| Hanssen and Stub <sup>83</sup>             | 1   |     | 35   |                 |      |                | +        |         |
| Heeres <sup>84</sup>                       | 1   |     |      |                 |      |                | +        |         |
| Kerppola <sup>27</sup>                     | 2   | f   | 30   |                 |      |                | +        |         |
|  |   | f   | 37   |                 |      |                | +        |         |
| Landstrom <sup>86</sup>                    | 1   |     |      |                 |      |                |          |         |
| Lichtenstein <sup>66</sup>                 | 1   | f   |      | 114             |      |                |          | +       |
| Meulengracht <sup>20</sup>                 | 8   | f   | 30   | 151             |      |                | +        |         |
|  |   | f   | 30   |                 |      |                | +        |         |
|  |   | f   | 35   |                 |      |                | +        |         |
|  |   | f   | 39   |                 |      |                | +        |         |
|  |   | f   | 53   |                 |      |                | +        |         |
|  |   | f   | 58   |                 |      |                | +        |         |
|  |   | f   | 58   |                 |      |                | +        |         |
|  |   | f   | 62   |                 |      |                | +        |         |
| Murphy <sup>25</sup> *                     | 18  |     |      | 578             |      |                | +        |         |
| Neusser <sup>86</sup> †                    | 1   |     | 44   |                 |      | +              |          |         |
| Schroll <sup>87</sup>                      | 1   | m   | 26   |                 |      |                | +        | +       |
| Schur <sup>88</sup>                        | 1   |     |      |                 |      |                |          | +       |
| Schwanke <sup>6</sup>                      | 1   | f   | 54   |                 | 52   |                | +        |         |
| Stenstam <sup>31</sup>                     | 8   | m   | 44   | 192             | 389  | +              |          | +       |
|  |   | f   | 33   |                 |      |                |          |         |
|  |   | f   | 35   |                 |      | +              |          |         |
|  |   | f   | 43   |                 |      |                | +        |         |
|  |   | f   | 46   |                 |      | +              |          |         |
|  |   | f   | 58   |                 |      |                | +        |         |
|  |   | f   | 58   |                 |      |                | +        |         |
|  |   | f   | 72   |                 |      |                | +        |         |
| Troll <sup>89</sup>                        | 1   |     |      |                 |      |                |          |         |
| Vedder <sup>76</sup>                       | 1   | m   |      |                 |      |                | +        |         |
| Weese <sup>90</sup>                        | 1   | f   | 61   | 370             |      |                | +        |         |
| Wilkinson <sup>34</sup>                    | 3   |     |      |                 |      | +              |          |         |
|  | 75  |     | 2603 | 1621            |      |                |          |         |

\* Murphy states only that exophthalmic goiter was the first disease in eight cases.

† Same case was published by Chvostec and by Decastello.

TABLE III  
Incidence of the Combination of Pernicious Anemia and Hyperthyroidism

|                                   | Total no. admissions to hospital | No. cases pernicious anemia | No. cases Graves' disease | No. cases Graves' disease and pernicious anemia |
|-----------------------------------|----------------------------------|-----------------------------|---------------------------|---|
| Andrus and Wintrobe <sup>22</sup> | 30,208                           | 335                         | 626                       | 2   |
|                                   | 19,535                           | 95                          | 504                       | 3   |
| Stenstam <sup>21</sup>            | 28,411                           | 192                         | 389                       | 3   |
| Totals                            | 78,154                           | 622                         | 1519                      | 8   |

Analysis of table 2 indicates that the incidence of hyperthyroidism in pernicious anemia is only 0.6 per cent, whereas the incidence of pernicious anemia in hyperthyroidism is 1.9 per cent. Stenstam <sup>21</sup> and Andrus and Wintrobe <sup>22</sup> surveyed the number of cases of pernicious anemia and hyperthyroidism occurring separately and in combination, and compared these with the total hospital admissions (table 3). From their data we can calculate the correlation factor to be 0.005, i.e., mathematically a real relationship is improbable.

We present here in detail an interesting coincidence of hyperthyroidism and pernicious anemia in an elderly female whom we have had the opportunity of observing closely over 20 months of continuous hospitalization.

#### CASE REPORT

C. C., a 65 year old white female, was first admitted to the Metropolitan Hospital on October 21, 1942 complaining of extreme weakness, dyspnea, palpitation, headache, tinnitus, and blurred vision. These symptoms, which had their onset shortly after the death of her husband five years previously, were markedly aggravated in the few weeks prior to admission, and were occasionally associated with vomiting. Of note in the past history were two operations: the first one a bilateral ovariectomy at the age of 26, the reason for which is unknown, and the second a subtotal thyroidectomy at the age of 58 for hyperthyroidism.

Physical examination revealed a chronically ill, thin, pale elderly white female who was confused and disoriented. The mucous membranes were pale; the tongue was smooth, pink, and uncoated. In the region of the thyroid gland there was a well-healed collar incision underneath which a small amount of thyroid tissue was palpable. The cardiac sounds were regular and of good quality, with a moderate accentuation of the second aortic sound; a loud blowing systolic murmur was audible over the whole precordium. The lungs were clear. The liver and spleen were not palpable. The deep tendon reflexes were hypoactive, but no pathological reflexes were elicited.

A blood count showed 40 per cent hemoglobin, with 1.6 million erythrocytes and 3,650 leukocytes per cu. mm., and a differential white count of which polymorphonuclears comprised 45 per cent, lymphocytes 48 per cent, and monocytes 8 per cent. The sternal marrow was diffusely megaloblastic. The icteric index was 8.5, and the van den Bergh reaction was of the direct, delayed type. On gastric analysis, no free hydrochloric acid was found.

The patient responded well to the administration of liver extract and small transfusions. Her sensorium cleared, strength returned, and the symptomatology present on entry disappeared. She was discharged to the Out-Patient Department on November 19, 1942, where her pernicious anemia was satisfactorily treated until February 6, 1943. On the latter date she was returned to the hospital complaining of marked

nervousness, dizziness, tingling in the extremities, weakness, dyspnea, palpitation, and insomnia.

Physical examination then revealed a hyperkinetic, apprehensive elderly woman, well oriented for time and place. Marked exophthalmos was present, with moderate lid-lag and difficulty in convergence. There was a gross tremor of the hands, but the deep tendon reflexes were hypoactive. Hypesthesia was present in both feet, and the vibratory sense was diminished over the lower leg. The remainder of the examination was not remarkable.

Her basal metabolic rate, which had been plus 70 per cent in the clinic several days before admission, was now plus 34 per cent. The findings on examination of the blood were hemoglobin 80 per cent, and 5.93 million erythrocytes and 5,600 leukocytes per cu. mm., with a differential white cell count of 50 per cent polymorphonuclears, 46 per cent lymphocytes, and 4 per cent monocytes. The blood sugar, urea nitrogen, and creatinine levels were within normal limits. Gastric analysis again yielded no free hydrochloric acid, even after injection of histamine. Roentgenograms of the skull demonstrated a normal sella turcica and normal clinoid processes. In the electrocardiogram, many auricular and ventricular extrasystoles were noted. The circulation time, performed by the fluorescein method of Lange,<sup>36, 37</sup> was 15 seconds from arm to lip, and 31 seconds from arm to leg.

Injection of liver extract at this time was immediately followed by a sensitivity reaction characterized by marked itching and flushing, both immediately relieved by the intravenous administration of calcium gluconate. As the blood picture subsequently remained within normal limits, no further injection of liver was attempted.

Because the patient was opposed to operation and because we thought that her hyperthyroidism might be secondary to pituitary overactivity, she was given desiccated thyroid, gr. 1/10 daily. Some clinical improvement was noted, despite the fact that the basal metabolic rate on February 25 was plus 53 per cent. Subsequent determinations, made at approximately monthly intervals, ranged between plus 28 per cent and plus 63 per cent.

Early in April, of 1943, the patient showed signs of mental confusion, later becoming irrational, disoriented, and finally stuporous. About this time, too, auricular fibrillation developed, which persisted for more than one year. Examination of the peripheral blood and of the bone marrow revealed no abnormalities. The patient was given 50 mg. each of thiamin chloride, nicotinamide, and cevitamic acid intravenously daily for four days, with a complete return to consciousness and clearing of the sensorium. Adequate vitamin supplements were thereafter continued by mouth.

During the succeeding six months, the patient's status changed little; there was no weight loss and few subjective complaints, in spite of a persistently elevated basal metabolic rate. During November and December, 1943, the clinical signs of hyperthyroidism increased; weight loss, irritability, marked perspiration, and tremor. Therefore, in January, 1944, thiouracil 0.4 gm. daily, was prescribed, following which a complete remission of all symptoms and signs of hyperthyroidism occurred. The basal metabolic rate fell to plus 4 per cent, and the auricular fibrillation was replaced by a normal sinus rhythm. The details of the patient's course during thiouracil therapy are more fully reported elsewhere.<sup>38</sup>

#### DISCUSSION

The sequence of events in the above case is rather interesting. It is clear that the hyperthyroidism was present a considerable period of time before the pernicious anemia occurred. Following sub-total thyroidectomy, the metabolic status remained normal for seven years, during which pernicious anemia made its appearance. The second episode of hyperthyroidism developed while the

pernicious anemia was regressing under treatment with injections of liver extract. It is noteworthy that the pernicious anemia continued into full remission in the face of a full-blown hyperthyroidism, which of itself might have been expected to produce a pseudo-pernicious anemia picture. It is of no great moment that the patient did not require more liver injections to maintain a normal blood picture after they were discontinued in February, 1943, as a result of sensitivity. It is well known that patients with pernicious anemia remain clinically well after a few initial doses of liver; in fact, spontaneous remissions are not uncommon.

That the nutritional needs of the body may be greatly increased by hyperthyroidism is forcefully illustrated by the stuporous state our patient developed in April, 1944. The condition simulated that of an advanced arteriosclerotic cerebral degeneration and was only completely differentiated from it when it was dramatically relieved by parenteral vitamin therapy. Although the increased needs for vitamins A and B<sub>1</sub> in hyperthyroidism have been well established, little attention has been devoted to a study of nicotinic acid, the use of which had such a striking effect in our patient.

The simultaneous occurrence of hyperthyroidism and pernicious anemia naturally raises the question of the influence of each disease upon the other.

*Some Physiologico-Pathologic Considerations of Thyreo-Hematopoietic Relationships.* Since many authors have discussed the influence of the thyroid gland on blood formation, it is surprising that the bone marrow has not been examined more frequently in uncomplicated hyperthyroidism. Only 10 cases are reported wherein such examinations were performed. In two of these cases,<sup>39</sup> only the ribs were examined, and these were found to be normal. Of the others, seven showed red bone marrow.<sup>40, 41, 42, 43, 44</sup> In Rautmann's case<sup>42</sup> the extremely large number of eosinophilic myelocytes was striking, as was the moderate number of erythroblasts. There were no findings *in vivo* to explain the presence of red bone marrow. One of Pettavel's patients, who also had red bone marrow, exhibited a normal blood picture while alive.<sup>39</sup> Wegelin<sup>45</sup> described yellow marrow in one case. Despite the hyperplasia of the marrow noted in more than half these cases, a direct effect of the thyroid on the bone marrow was not established.

Nor is the influence of the thyroid on blood formation clearly illustrated by cases of hyperthyroidism combined with pernicious anemia. Red marrow was noted in two such cases by Meulengracht<sup>30</sup> and in one case by Lichtenstein.<sup>46</sup> The latter also found atrophy of the pituitary and thyroid glands. Zondek<sup>16</sup> advocated the administration of thyroid powder in cases of anemia. It was asserted that some patients with pernicious anemia do not improve on liver therapy alone, but only after the addition of thyroid. Wilkinson,<sup>34</sup> however, felt there was "little evidence in favor" of the theory that thyroid substance was necessary for hemopoiesis.

On the other hand, a definite stimulation of the bone marrow by thyroid is claimed by some investigators in animal experiments. Parhon and Parhon<sup>47</sup> noted red bone marrow, cell proliferation, vasodilatation, and *les vesicules adipeuses*. Lida,<sup>48</sup> working with rabbits, considered the spleen necessary for proper stimulation of the marrow. Mansfeld<sup>50</sup> claimed the existence of a second thyroid hormone the action of which is primarily upon the bone marrow.

Kunde, Green, and Burns<sup>51</sup> studied the influence of thyroid feeding on rab-

bits, and noted an initial polycythemia and increase in hemoglobin. The bone marrow was "less fatty than normal." Besides the polycythemia, they also observed many eosinophiles and myelocytes. Lim and Brown<sup>52</sup> noted bone marrow stimulation only in young rabbits.

The observations of Marine<sup>53</sup> are of great importance. He produced hypertrophy of the thyroid in fishes and in rats by feeding them liver one to three days old. Animals receiving either fresh liver or liver four to six days old maintained normal or nearly normal thyroid glands. Marine concluded that "the diet is only a contributing factor, and it may act by increasing the work of the thyroid in order to maintain a general increase in metabolism, especially in connection with the overfeeding of nutritionally incomplete diets."

In some cases of pernicious anemia, the thyroid gland was examined post mortem. It was found enlarged once in 30 cases reported by Neumann.<sup>54</sup> In 13 cases reported by Mendershausen,<sup>55</sup> only one had a normal thyroid; in the remainder, the gland was atrophic and infiltrated with lymphocytes, and new colloid was sometimes present. Kerppola<sup>27</sup> noted enlargement of the thyroid gland in five of 107 patients with pernicious anemia. Schaumann and Saltzman<sup>26</sup> made similar observations.

In two cases of pernicious anemia, Holler<sup>56</sup> found no iodine in the thyroid. This is of interest because of his claim<sup>57</sup> to have found a hemolysin in the blood of hyperthyroid patients "which (is) similar to that in cases of pernicious anemia and acts as a hemo- and myelotoxic agent." Pappenheim has propounded a similar theory.<sup>58</sup>

Employing the hippuric acid test, Bartels and Perkin<sup>59</sup> found that hepatic damage in exophthalmic goiter was more frequent and more severe than had previously been suspected. Similar results were reported by Haines, Magath, and Power.<sup>60</sup> Rowe<sup>61</sup> found hepatic dysfunction in 22.4 per cent of 664 cases, far more than in any other endocrinopathy. Pende,<sup>62</sup> too, noted hepatic damage in Graves' disease; he also found the same abnormalities of the leukocytes in hyperthyroidism as in pernicious anemia.

Pathological examinations of the liver in Graves' disease are quite striking. Haban<sup>63</sup> speaks of "cirrhosis Basedowii." Cameron and Karunaratne<sup>64</sup> observed changes in hepatic structure in 20 of 30 cases. Weller<sup>65</sup> studied a group of 48 cases in which all possible causative factors of hepatitis were eliminated. Sixteen showed slight chronic hepatitis, and 26 exhibited marked involvement; the structural changes varied from chronic hepatitis to necrotizing processes. Beaver and Pemberton<sup>66</sup> reported similar findings.

*Age and Sex Incidence of Hyperthyroidism and Pernicious Anemia.* There is a difference in the age incidence of pernicious anemia and Graves' disease. Patients with hyperthyroidism are under 20 or between 20 and 40 years old, according to Goldzieher<sup>67</sup> and Deusch,<sup>68</sup> whereas those with pernicious anemia are usually between the ages of 40 and 60.<sup>69</sup> Murphy<sup>35</sup> found the average age of patients with pernicious anemia to be 55 years. In 72 per cent of his cases, the disease was discovered after the fiftieth year.

Exact statements about age and sex are available in 37 patients reported to have both pernicious anemia and hyperthyroidism. Thirty were female, five male, and two were not specifically designated. A majority of the patients were between 30 and 50 years old (table 4), with the males averaging 32.4 years, and

TABLE IV  
Age Distribution in Patients Suffering from Pernicious Anemia and Hyperthyroidism

| Age    | Sex |    |   | Total |
|--------|-----|----|---|-------|
|        | M.  | F. | ? |       |
| 15     | 1   |    |   | 1     |
| 20-29  | 2   | 1  |   | 3     |
| 30-39  |     | 11 | 1 | 12    |
| 40-49  | 1   | 7  | 1 | 9     |
| 50-59  | 1   | 7  |   | 8     |
| 60-69  |     | 3  |   | 3     |
| 72     |     | 1  |   | 1     |
| Totals | 5   | 30 | 2 | 37    |

the females 45.1 years. Sixteen of the 37 patients were younger than 40 years. It is apparent, then, that pernicious anemia becomes manifest earlier than usual if it is combined with hyperthyroidism.

*The Reciprocal Influence of Hyperthyroidism and Pernicious Anemia upon Each Other.* Of the 75 patients whose histories are summarized (table 2), statements are available on the first disease diagnosed in only 56 cases. Forty-two (75.0 per cent) showed evidence of hyperthyroidism prior to the onset of pernicious anemia; 10 (17.9 per cent) presented the reverse sequence of events; and four (7.1 per cent) apparently developed both diseases simultaneously.

When hyperthyroidism was the first disease diagnosed, pernicious anemia made its appearance any time between one and 30 years later, the average being 15.5 years. When pernicious anemia was the initial disease, hyperthyroidism supervened from one-half to nine years later, with an average of four years.

It has been stated by various authors that the course of either hyperthyroidism or pernicious anemia is not changed by the superimposition of the other. Giffin and Bowler,<sup>33</sup> for example, say "There was nothing to indicate . . . a modification of the course of either disease." Others, however, like Meulengracht,<sup>30</sup> assert that the symptoms of Graves' disease more or less disappeared after the development of pernicious anemia.

In the published case histories, data are available in 49 instances on the thyroid manifestations present when pernicious anemia was diagnosed; these are detailed in table 5. A critical analysis of the figures in this table reveals

TABLE V  
Thyroid Manifestations Present When the Diagnosis of Pernicious Anemia Was Made (49 cases)

|   | No. times observed | Per cent |
|---|--------------------|----------|
| Exophthalmos only . . . . .                           | 7                  | 14.3     |
| Increased basal metabolic rate . . . . .              | 14                 | 28.6     |
| Remaining manifestations of Graves' disease . . . . . | 7                  | 14.3     |
| All symptoms of Graves' disease . . . . .             | 7                  | 14.3     |
| No symptoms of Graves' disease . . . . .              | 11                 | 22.4     |
| Hypothyroidism had developed <sup>1</sup> . . . . .   | 3                  | 6.1      |
| Total . . . . .                                       | 49                 | 100.0    |

<sup>1</sup> In one case of Kerppola<sup>27</sup> it is not certain whether or not a hypofunction of the thyroid had developed.

that the number of cases in which Graves' disease existed when the second disease was diagnosed is actually smaller than appears at first glance. For example, it is known that exophthalmos is one of the most difficult manifestations to influence, and that it frequently persists after the hyperthyroidism is completely cured clinically. Thus it may be assumed that the seven patients having only exophthalmos, had no real evidence of hyperthyroidism.

Similar caution must be exercised in interpreting basal metabolic rates. Elevated percentages are listed in 14 instances; the figures given by Murphy<sup>35</sup> are excluded, since he merely stated that the values ranged between plus 20 per cent and plus 62 per cent. In the tabulated cases, the basal metabolic rate varied between plus 15 per cent and plus 114 per cent, with an average of 42.3 per cent. Since Becker<sup>70</sup> pointed out that the basal metabolism in pernicious anemia alone may be increased to as high as plus 28 per cent, we cannot diagnose hyperthyroidism when pernicious anemia is also present if the rate is below plus 30 per cent. On this basis, five of the 14 tabulated cases must be excluded. Furthermore, we may presume that three of the 49 patients had developed a hypofunction, and in seven it is questionable whether signs of hyperfunction still existed. Thus, the diagnosis of hyperthyroidism is doubtful in almost half the cases, and the ameliorating effect of the supervening pernicious anemia is questionable.

Of further interest is the fact that Meulengracht,<sup>30</sup> Murphy,<sup>35</sup> and others expressly state that their patients never developed features of myxedema if pernicious anemia were present with the hyperthyroidism. An obvious hypofunction existed in only three, perhaps four, cases. In one of Murphy's cases the basal metabolic rate dropped to minus 26 per cent, and in one of Adler's<sup>71</sup> from plus 67 per cent to minus 27 per cent. In the case observed by Gulland and Goodall,<sup>72</sup> "the symptoms (of Graves' disease) had given place to those of myxedema" shortly before pernicious anemia developed. Similar doubts exist concerning the direct influence of pernicious anemia in Kerppola's patient.<sup>27</sup>

On the other hand, there is less question about the influence exerted by the development of hyperthyroidism in cases of preëxistent pernicious anemia. It is recognized that the symptoms of this blood disease may be replaced by an entirely new symptom complex; such transformations were emphasized by Naegeli<sup>69</sup> in one case of tuberculosis and in one of heart failure, and by Weinberg<sup>73</sup> in a patient who developed cancer of the stomach. The most characteristic feature in patients with pernicious anemia after the development of Graves' disease is the loss of weight. Pathological pigmentation has also been observed.<sup>30</sup> However, each of these alterations can be attributed to Graves' disease alone, without necessarily implying that the antecedent pernicious anemia played a part.

*Etiological Factors in Hyperthyroidism and Pernicious Anemia.* Theories on the pathogenesis of each of the two diseases individually are manifold, but only those will be mentioned which perhaps indicate the relationship of the one to the other. For example, one group of authors considered a constitutional basis, e.g., Meulengracht, whereas others, like Stenstam,<sup>31</sup> denied its importance. The physical features of patients with pernicious anemia are quite different from those with Graves' disease. The latter are young, slender, and lose weight easily. The former are older, rather stout, and exhibit no tendency to weight loss.

Furthermore, if the two diseases were genetically related, one should expect them to occur frequently in a given family. As far as we could determine, there

have been only three histories published in which both diseases occurred in the same family. Reference has already been made to one, mentioned by Murphy.<sup>35</sup> Another, reported by Hirsch,<sup>74</sup> concerned a patient with pernicious anemia; one sister died of pernicious anemia, while another suffered from Graves' disease. The third instance, reported by Benjamin,<sup>75</sup> was that of a patient with pernicious anemia and diabetes mellitus whose mother had an extremely severe thyrotoxicosis. One of us (F. B.) had occasion to treat a patient with hyperthyroidism whose mother, grandfather, and two paternal uncles died of pernicious anemia.

Vedder<sup>76</sup> considered Graves' disease to be a deficiency state; moreover, he attributed the pathogenesis of pernicious anemia to a diet poor in protein. In stressing the similarity of the two processes, he emphasizes diarrhea, achylia, and increased basal metabolic rate as common to both. Pappenheim<sup>58</sup> noted the occurrence of pernicious anemia following shock or toxicosis, an etiology quite common in thyrotoxicosis. Pende<sup>62</sup> emphasized the similarity of the white blood cell picture in the two diseases.

The etiologic rôle of achlorhydria in the anemias of hyperthyroidism is not convincing, even though achylia does occur in cases of long-standing Graves' disease. Hansen,<sup>77</sup> Meulengracht,<sup>30</sup> and Fleischhans<sup>74</sup> suggest, rather, that it may be *one* factor which makes pernicious anemia manifest (without actually being a direct cause). A contributory rôle may also be played by the hepatic damage found in Graves' disease, especially when combined with achlorhydria.

The question has been raised whether the second disease, be it pernicious anemia or hyperthyroidism, is caused by the therapy used for the first. Some authors have felt that the treatment of pernicious anemia by liver may be responsible for subsequent hyperthyroidism, but the evidence at best is tenuous. In a few instances where pernicious anemia followed hyperthyroidism, radiation of the thyroid may have been responsible, perhaps by producing myxedema and its attendant pernicious anemia-like picture. Hansen,<sup>77</sup> for example, observed the development of pernicious anemia "acutely, directly after a course of roentgen treatment. The causal connection seemed unquestionable, although pre-existing achylia may have afforded a predisposition." Similar instances have been noted after thyroidectomy, but in none of them can other factors be excluded.

If all factors are critically analyzed, it becomes apparent that the co-existence of hyperthyroidism and pernicious anemia is only fortuitous, and that no demonstrable causal relationship exists.

#### SUMMARY AND CONCLUSIONS

Seventy-six cases, including that herein reported, of co-existent hyperthyroidism and pernicious anemia have been published in the literature; of these, 50 were described by six authors.

Three-fourths of all these patients exhibited evidence of hyperthyroidism before the onset of symptoms of pernicious anemia. Ten presented the reverse sequence. Four apparently developed both diseases simultaneously.

A secondary hypofunction of the thyroid developed in only three cases following the onset of pernicious anemia, and hyperfunction disappeared in a number of others.

Roentgen therapy of the thyroid in Graves' disease may be of causal significance for the development of pernicious anemia in a very few cases, but the theories of association advanced by various authors are not convincing. Some

stress the achlorhydria, others the liver damage, and still others the constitutional factor.

The long interval between the development of the two diseases, and the extremely low correlation factor afford no support for a cause-effect relationship between them. Further studies of the influence of the thyroid gland on blood formation are necessary before definite conclusions can be reached.

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### HEMOLYTIC ANEMIA, HYPERGLOBULINEMIA AND BOECK'S SARCOID \*

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HEMOLYTIC anemia, first described in 1900 by Minkowski<sup>1</sup> and associated with jaundice, increased fragility of the red cells, and spherocytosis, may occur as a congenital disease or may be acquired. Dameshek<sup>2</sup> lists chemicals (including sulfa drugs), immune bodies (erythroblastosis fetalis) and various infections and diseases as being responsible for the acquired form. Singer and Dameshek<sup>3</sup> reported cases occurring with a dermoid cyst of the ovary, chronic lymphatic leukemia, Hodgkin's, lymphosarcoma, liver disease and pneumonia. Wintrobe<sup>4</sup> refers to reports in the older literature of its occurrence with syphilis, tuberculosis, streptococcal septicemia, paratyphoid fever, cirrhosis of the liver and pregnancy. More recent reports mention sarcoma of the spleen, reticulo-endotheliosis, salmonella infection, plumbism, liver disease, and hyperthyroidism in addition to those reported by Singer and Dameshek.<sup>3</sup>

We have encountered a case with recurrence after splenectomy and death in a hemolytic crisis which was associated with Boeck's sarcoid. This case is of particular interest and importance in the light of cases reported by Kracke and Hoffman<sup>5</sup> and Jeghers and Selesnick<sup>6</sup> which had a hyperglobulinemia as did our case. Haden<sup>7</sup> has also reported one associated with probable sarcoid. Our case represents the first instance of hemolytic anemia associated with Boeck's sarcoid proved by autopsy findings.

#### CASE REPORT

*Present Illness.* Mrs. H. H., a 46 year old white female, was first seen by a physician in September 1944, complaining of pallor, jaundice, weakness, drowsiness and tinnitus in the right ear. This followed immediately upon a two week period during which she had three to four drinks each night. Fifteen years previously there had been an episode of jaundice, nausea, vomiting and abdominal pain following excessive indulgence in alcohol. The episode lasted a few weeks and was regarded as a gall-bladder disturbance. With the present illness she was hospitalized and gastrointestinal and gall-bladder roentgenograms were done which were negative. During this period she had three transfusions but without significant improvement. She remained weak with fainting spells and tachycardia on slight exertion. Her

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stools were never gray or white. Her hemoglobin is reported to have been 65 per cent. She was referred to physicians in New York where, after blood studies showing anemia, spherocytosis, reticulocytosis and increased red cell fragility, a diagnosis of hemolytic anemia was made and a splenectomy done on January 2, 1945. Following this the jaundice cleared, the blood findings returned to normal and the clinical symptoms disappeared. About two months later (February 28, 1945) she was admitted to this hospital, again complaining of tinnitus, jaundice, and weakness of increasing severity for one week.

*Physical Examination* (February 28, 1945). Temperature 101° F., pulse 110, respirations 22, blood pressure 145 mm. Hg systolic and 80 mm. diastolic. The patient was a jaundiced, moderately dyspneic white female about 46 years of age. There were no skin rashes and no enlargement of the peripheral lymph nodes. The only

TABLE I  
Hematological Chart

|                                  | 12/26   | 1/2     | 1/7     | 1/18    | 2/28    | 3/1      | 3/3   |
|----------------------------------|---------|---------|---------|---------|---------|----------|-------|
| Hemoglobin—%                     | 41      | 60      | 73      | 80      | 23      | 32       | 20    |
| —gm.                             |         |         |         |         | 3.9     | 5.4      | 3.5   |
| RBC (millions)                   | 1.81    | 3.34    | 4.1     | 4.56    | 1.36    | 1.43     | 1.58  |
| Nucleated Cell Count (thousands) | 15.6    | 12.3    | 10.2    | 8.3     | 56.0*   | 73.6*    | 66.4* |
| Stem Cells                       |         |         |         |         | 7       |          | 5     |
| Red Series—                      |         |         |         |         |         |          |       |
| Spherocytosis                    | 4+      | 4+      | 0       | 0       | 4+      | 4+       | 4+    |
| Reticulocytes %                  | 44      |         |         | 1       | 12      |          |       |
| Normoblasts                      | Many    |         |         |         | 33      |          | 37    |
| Erythroblasts                    |         |         |         |         | 14      |          | 12    |
| Megaloblasts                     |         |         |         |         | 4       |          | 4     |
| White Series—                    |         |         |         |         |         |          |       |
| Neutrocytes                      | 47      | 54      | 51      | 66      | 25      |          | 23    |
| Bands                            | 7       | 10      | 9       | 6       | 1       |          | 3     |
| Myelocytes                       | 1       | 0       | 0       | 0       | 0       |          | 0     |
| Lymphocytes                      | 34      | 30      | 30      | 19      | 5       |          | 5     |
| Monocytes                        | 8       | 4       | 8       | 7       | 0       |          | 0     |
| Eosinocytes                      | 2       | 2       | 2       | 1       | 0       |          | 0     |
| Basocytes                        | 1       | 0       | 0       | 1       | 0       |          | 0     |
| Platelets                        | 150,000 | 280,000 | 240,000 | 480,000 | Normal  |          |       |
| Red Blood Cell Fragility         | .52-.38 |         |         |         | .50-.28 |          |       |
| Rh                               |         |         |         |         |         | Positive |       |

\* 50% of the nucleated cells are erythropoietic forms.

findings of note were the jaundice, a splenectomy scar in the left upper quadrant of the abdomen and the occurrence of a soft apical systolic murmur.

*Laboratory.* The hematological findings are indicated in table 1. A bone marrow aspiration done in January showed a marked erythroblastic and normoblastic hyperplasia, 78 per cent of the cells being erythropoietic forms. Blood coagulation and prothrombin times were normal. The stools were negative for blood, ova and parasites. In January the urine showed urobilinogen in dilutions varying from 1 to 10 to 1 to 40 and no bilirubin was present. In February the urobilinogen was markedly increased. The blood Wassermann reaction was negative. The blood cholesterol in January was 280 mg. with esters of 195. A galactose tolerance test was normal but the cephalin-flocculation gave a 1+ result. The total protein in January was 5.4 with 3.6 per cent albumin and 1.8 per cent globulin, but in March it was 7.6 with an albumin of 3.6 per cent and a globulin of 4.0. The direct Van den Bergh was negative. The icteric index was 27 in January and 40 in March.

The spleen removed surgically weighed 485 gm. Grossly it was dark red and

firm. Microscopically it showed marked congestion of the sinusoids and widely separated small follicles. There were no perifollicular hemorrhages or empty sinusoids but the general picture was consistent with the changes found in hemolytic anemia. No foci of necrosis or tubercles were noted.

*Course.* During her brief stay in this hospital an attempt was made to improve the patient's condition with repeated small transfusions. There were no transfusion reactions but no significant changes in the blood findings were produced. There was a progressive increase in the temperature to 104° F. with increasing weakness and dyspnea and the patient died of anoxemia on the fifth hospital day.

*Autopsy. Gross:* Only the positive findings are given. On inspection there was moderate jaundice, a healed surgical scar in the left upper quadrant of the abdomen

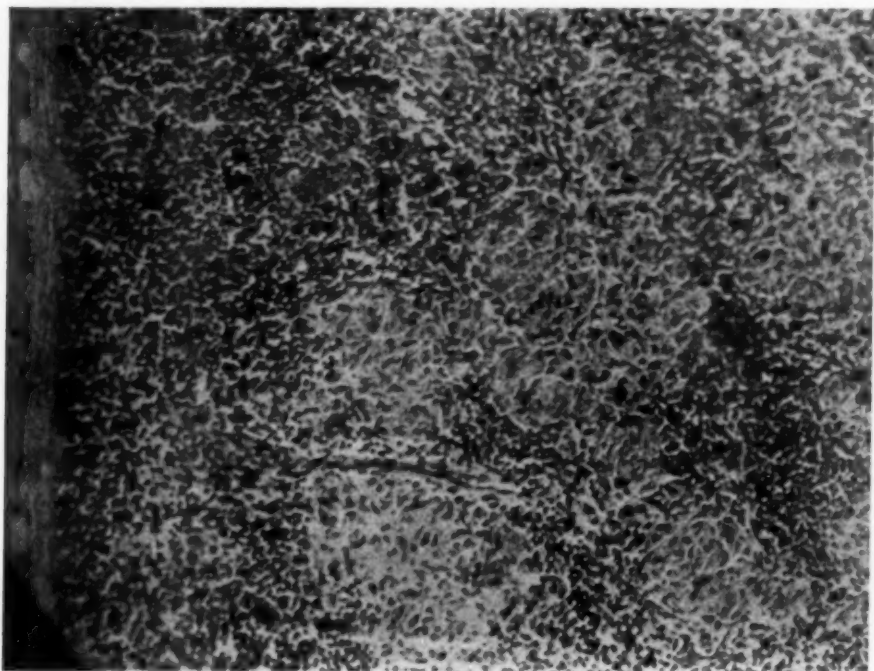


FIG. 1. Lymph node showing multiple discrete tubercle-like lesions (sarcoid) composed of giant cells, monocytes and fibroblasts. Phloxine methylene-blue.  $\times 100$ .

and a mild edema of both ankles. The peritoneal, thoracic and pericardial cavities were normal. The heart weighed 360 gm. and was normal save for a yellow mottling of the endocardium of the left ventricle. The lungs were normal and there was no evidence of tuberculosis. The spleen was absent, but buried in the periadrenal fat on the left side there were three round red firm nodules measuring 1.2, 0.4, and 0.7 cm. in diameter. The pancreas and gastrointestinal tract were normal. The liver weighed 1800 gm.; externally it was red-brown and smooth and on section it cut with normal resistance to reveal a firm brown surface with a diffuse pale grayish-yellow mottling. The bile ducts were normal but the gall-bladder contained 50 c.c. of thick black mucoid material and innumerable small, soft, black calculi measuring up to 0.2 cm. in diameter. The right adrenal was normal but the left contained a soft yellow cortical nodule 2.5 cm. in diameter. The kidneys, bladder and genital organs were

normal. The vertebral, rib and sternal marrows were dark red, jelly-like and soft. There was moderate enlargement (three to four times) of the tracheobronchial, para-aortic and pancreatico-lienal lymph nodes, all of which presented soft gray-white slightly granular surfaces. The peripheral lymph nodes were not enlarged.

*Microscopic:* There were foci of erythropoiesis in the lung, kidneys, liver and lymph nodes composed of stem cells, erythroblasts and normoblasts. The red nodules in the periadrenal fat were composed of splenic elements containing sinusoids which

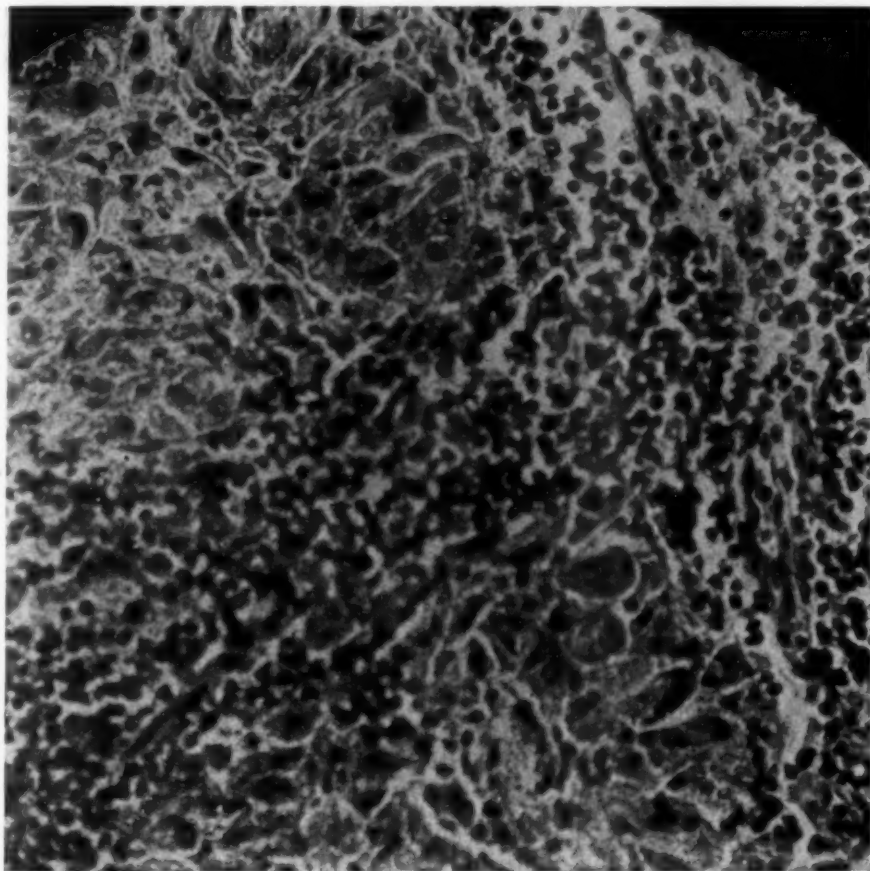


FIG. 2. Lymph node showing the detail of the sarcoid lesions under higher magnification. Phloxine methylene-blue.  $\times 400$ .

were markedly engorged and small lymph follicles with central arterioles of the type encountered in splenic tissue. The tracheobronchial, para-aortic and pancreatico-lienal lymph nodes were almost completely replaced by discrete, small tubercle-like lesions composed of a central mass of collagen and lymphocytes and surrounded by swollen eosinophilic monocytes (epithelioid cells), fibroblasts and occasional multinucleated giant cells (figures 1 and 2). Special stains for tubercle bacilli were negative and concentrates from the nodes were also negative for tubercle bacilli. Similar lesions were present in the sternal bone marrow (figures 3 and 4). All marrows

showed complete replacement of the fat by hematopoietic elements, the erythropoietic foci being markedly increased and erythroblasts and normoblasts dominating. The adrenal nodule was composed of typical, foamy, adult cortical cells. Sections from all of the other organs showed no significant changes.

*Pathological Diagnoses:* Findings consistent with hemolytic anemia: (a) icterus, (b) erythroid hyperplasia of bone marrows, (c) erythroblastemia, (d) spherocytosis, (e) increased red cell fragility, (f) extra-medullary hematopoiesis of liver, kidney,

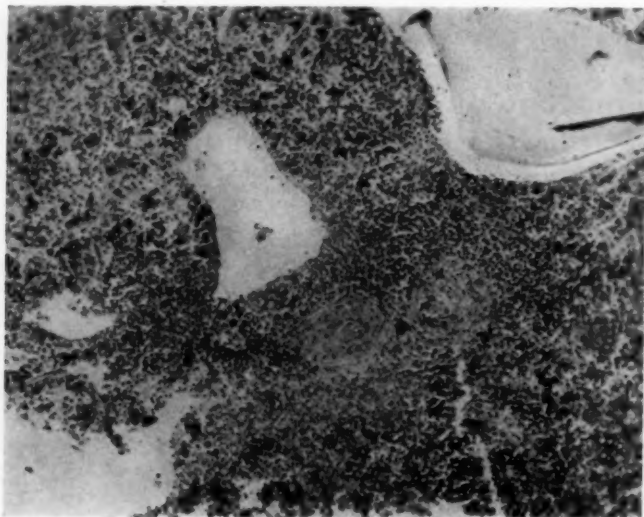


FIG. 3. Bone marrow showing two tubercle-like lesions (sarcoid) similar to those of the lymph nodes. Hyperplasia is also evident in the replacement of the fat by hematopoietic elements. Note the numerous erythropoietic foci appearing as clumps of black dots. Phloxine methylene-blue.  $\times 50$ .

lung and lymph nodes; cholelithiasis (pigment); Boeck's sarcoid with involvement of lymph nodes and bone marrow; accessory splenic tissue; cortical adenoma of adrenal.

#### DISCUSSION

This case is typical, from the clinical, clinical-pathological and morphological findings, of hemolytic anemia. Whether it is of the congenital type with recurrence due to the small amount of accessory splenic tissue or of the acquired type and secondary to the sarcoidosis are points which may be debated. In any case it is of importance and interest.

The volume of splenic tissue was extremely small, totaling less than 2.0 cubic centimeters. This is of importance in consideration of the mechanisms postulated in the production of hemolytic anemia. Ham and Castle<sup>8</sup> have suggested that an important factor is stasis of blood in the spleen. In this case it is hardly conceivable that splenic stasis could be a factor when so little splenic tissue was present. We feel that if this case is to be regarded as the congenital type it presents strong evidence against the theory of stasis. On the other hand, one may readily conceive even a minute amount of tissue pro-

ducing the hemolysins that Dameshek and Schwartz<sup>9</sup> have described or the lysolecithins of Bergenhem and Fahraeus.<sup>10</sup>

We believe that the case is of the acquired type and is secondary to the Boeck's sarcoid. The lesions with collagenous necrosis, monocytes, fibroblasts, giant cells and the absence of tubercle bacilli are typical of sarcoid. The occurrence of the lesions of sarcoid in the various organs of the body including the lymph nodes and bone marrow has been described by Nickerson.<sup>11</sup> The diagnosis of sarcoid is substantiated by the increase in globulin (4.0) with a total protein of 7.6 gm. This occurrence of hyperglobulinemia is of particular im-

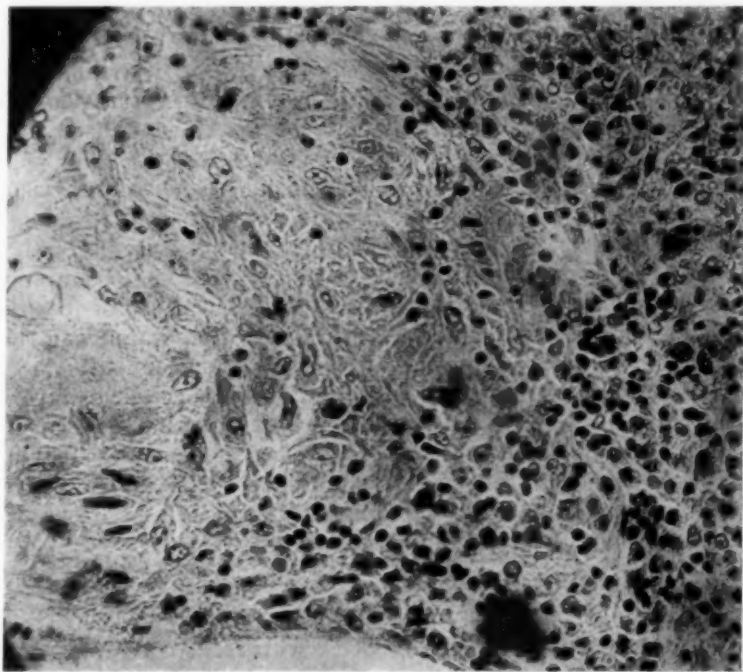


FIG. 4. Bone marrow showing the detail of the sarcoid lesions under higher magnification. Phloxine methylene-blue.  $\times 970$ .

portance inasmuch as there have been previous reports of hemolytic anemia with hyperglobulinemia. Jeghers and Selesnick<sup>6</sup> reported a case, but no studies were done on their patient with reference to a possible diagnosis of sarcoid. However, the case reported by Kracke and Hoffman<sup>5</sup> as "chronic hemolytic anemia with autoagglutination and hyperglobulinemia" adds to the significance of our findings. Their case was a 32 year old female with a five year history of fleeting arthritis, the joints being painful but not swollen. She had anemia, reticulocytosis and erythroblastic crises. The red cell fragility was normal but there was "suggestive spherocytosis." The total protein was 9.14 gm. with an albumin of 3.78 and a globulin of 5.26. Splenectomy was done but there was recurrence with an erythroblastic crisis and death. The autopsy was limited to a small incision but the findings in the liver are of particular interest.

"The liver weighed 2,000 gm. There was marked general atrophy of the hepatic cells with a small amount of fatty change. A single localized lesion having epithelioid cells, giant cells and a small amount of caseation necrosis was found. This resembled a miliary tubercle but acid-fast stains did not reveal organisms." The small granulomatous area was considered to be evidence of "chronic infection." They considered the case as an atypical chronic hemolytic anemia with autoagglutination and hemolysis secondary to chronic infection. The resemblance of the lesion to sarcoid was pointed out by the authors.

Hyperglobulinemia is a frequent finding in Boeck's sarcoid according to Middleton,<sup>12</sup> and the work of Harrell and Fisher<sup>13</sup> showed an increase in the total protein, particularly of the globulin fraction, often with reversal of the albumin-globulin ratio. We believe that the increase in globulin occurring in the case of Kracke and Hoffman<sup>5</sup> and our own is due to sarcoidosis and *not* the hemolytic anemia and that this may also be the explanation of the hyperglobulinemia occurring in the case of Jeghers and Selesnick.<sup>6</sup> We believe this because of the infrequency of hyperglobulinemia in hemolytic anemia and its frequent occurrence in sarcoidosis.

Haden<sup>7</sup> has described a case of hemolytic anemia secondary to sarcoid. The diagnosis of sarcoid was based upon radiological findings in the lungs, but its validity is open to question because of the uncertainty of the roentgenographic diagnosis of sarcoid and also because of the disappearance of the lesions after radio-therapy which is not the usual history of sarcoid. If Haden's case is accepted along with the one of Kracke and Hoffman and our own case, an association between Boeck's sarcoid and hemolytic anemia is indicated. However, it must be pointed out that in the acquired forms of hemolytic anemia there must be an additional intrinsic factor or abnormality as yet undetermined, for hemolytic anemia is an infrequent complication of any of the diseases that have been described as a precipitating cause.

#### CONCLUSIONS

1. A case of hemolytic anemia is reported with recurrence after splenectomy and death in an erythroblastic crisis, associated with hyperglobulinemia and Boeck's sarcoid with involvement of the lymph nodes and bone marrow.
2. Sarcoidosis is added to the list of conditions which may produce a hemolytic anemia of the acquired type.
3. Hyperglobulinemia occurring with hemolytic anemia is probably due to sarcoidosis rather than to the anemia.

We are indebted to Dr. Reuben Ottenberg of New York City for making available to us the findings on the patient while she was under observation in New York and to Dr. Paul Klemperer of the Mt. Sinai Hospital of New York City for allowing us to review the sections of the spleen. We are also indebted to Dr. Franklin Fite of the U. S. Public Health Service, Marine Hospital, Norfolk, Virginia for the photomicrographs.

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## EDITORIAL

### *POST-WAR MEDICAL EDUCATION*

THE sudden and unexpected end of World War II in August has given rise to a number of new problems in medical education which the medical schools and hospitals of this country were scarcely better prepared to meet than were industry and labor in general. Or more specifically, the following problems now confront us: (1) deceleration of the medical school program; (2) the admission of veterans to the medical schools; (3) post-graduate training of veterans who entered the medical service of the Army or Navy with hospital training inadequate to prepare them for the practice of medicine; and (4) clinical rehabilitation of older physicians and surgeons who, having held largely administrative positions in the Army or Navy, feel the need of refresher courses and active participation in clinical work before resuming their practice.

Under the Army Specialized Training Program and the Navy V-12 Program premedical students who qualified for such training were permitted only 18 to 20 months of college in which to complete the requirements for admission to medical school. This meant that many of the male students entering medical school during the war were 18 or 19 years of age, considerably younger than the average student entering medical school before the war. Furthermore, these youthful souls were at once plunged into an accelerated program of instruction whereby the four academic years of medical school were completed in three calendar years. It is certainly to the credit of these young men that they have maintained such a strenuous program as successfully as they have. Nonetheless, both students and faculty members are thoroughly in accord that deceleration of the medical school curriculum is highly desirable. The relatively long summer vacations of the pre-war era provided time for the students to "digest" the knowledge they had acquired, to make practical application of this knowledge by means of laboratory work or junior internships, and—of utmost importance to some—to earn money with which to defray the cost of their education. Deceleration must be contingent upon two factors, namely: the termination of the Army and Navy contracts with the medical schools and the abolition of the 9-9-9 plan for house officers in hospitals with a return to the 12-month internship in order that dates for commencing internship might dovetail with dates of graduation from medical schools. The Navy plans to terminate the V-12 program in the very near future, at which time the Navy students will return to civilian life as members of the inactive reserve and will be thrown "on their own" financially. These men will not be eligible for financial assistance under the "G.-I. Bill of Rights" unless they have had ninety or more days of active service with the Navy before entering medical school. Such a ruling seems a perfectly fair one since the government has already financed their

medical education completely besides paying these men regular maintenance salaries. The same rule will apply to the members of the A. S. T. P. when and if the Army returns them to an inactive status. So far the Army has given no indication as to when this will be. A number of the medical students inactivated from the services may find themselves financially embarrassed and, unless deceleration of the medical curriculum can be accomplished reasonably soon in order to provide summer vacations in which to earn money, scholarship and private loan funds will be taxed to the limit.

The admission of veterans to medical schools should be expedited in every way possible, since the majority of veterans who had partially or completely satisfied premedical requirements before entering the service will return to civilian life two or three years older than the average premedical student at a comparable stage in his training before the war. In view of this age factor, it would seem distinctly unfair to the veterans for medical schools to stiffen their requirements for admission at the present time. Rather, they might expect to return to their pre-war requirements by 1948 when the majority of qualified veterans who desire a medical education will already have gained admission to medical school. This would apply in particular to those schools which required a bachelor's degree prior to the war. In the writer's opinion, such schools would gain in respect what they might lose in prestige by admitting students during the next two years on the basis of the minimal amount of premedical training that was permitted during the war. Surely everything should be done to facilitate the medical education of those men who not only gave up several years of their lives but in many instances risked their lives in the service of their country.

Perhaps the most acute problem at the moment is the question of post-graduate training for young physician veterans who entered the medical corps of the Army or Navy with hospital training inadequate to prepare them for the practice of medicine, in many instances after an internship of only nine months. Relatively few of these young physicians had sufficient clinical work while in the service: some found themselves in purely administrative positions, others were assigned to very restricted fields of "medical activity"; and a number claim that they never actually saw a patient during their entire period of duty with the armed forces. These men will benefit little by didactic refresher courses. What they need is practical clinical experience in hospitals. To meet this need, the medical schools and hospitals are creating additional positions on the house staff, such as residencies and assistant residencies, externships, and fellowships exclusively designed for veterans. It is to be hoped that the "supply" of such positions will at least approximate the "demand." Veteran physicians who enter upon such a program of training are eligible for subsistence allotments under the G. I. Bill of Rights.

Lastly, we face the question of the "clinical rehabilitation" of older physicians and surgeons who have grown "rusty," as so many of them put it,

in largely administrative positions with the Army or Navy. For these men, refresher courses covering recent developments in diagnostic procedures, therapeutics, and operative technics will undoubtedly prove valuable, and such courses have been organized at a number of the larger medical centers. However, many of these older physicians will wish practical experience in hospitals before resuming their practice. All of us who have remained in civilian life during the war should do everything within our power to lend assistance to these most deserving individuals in the medical profession, the veteran physicians of World War II.

W. H. B.

## REVIEWS

*Medical Education in the United States before the Civil War.* By WILLIAM FREDERICK NORWOOD. Foreword by HENRY E. SIGERIST. 487 pages; 24 × 16 cm. University of Pennsylvania Press, Philadelphia. 1944. Price, \$6.00.

The author of this reference book, a medical historian, has done the history of American Medicine a great service by producing this absorbing, vivid, impartial and scholarly account of medical education in this country in the century before the Civil War.

In his preface, the author states that the study is not intended to be a technical consideration of the early teaching of medicine, but a survey of the rise and progress of the American system of medical instruction and the institutions of medical learning up to the time of the Civil War. He further states that it has been his intent to draw from obscurity many relatively unknown institutions. While the following is the author's concluding sentence, it epitomizes his objective: "Medical education in the United States, with all its ramifications, in the century before the Civil War, constitutes a significant and unique chapter in the social history of the country."

The work is divided into eight parts, the chapters of five of which describe in detail the various medical schools of the five geographic sections into which the author divided the country for purposes of his book. The other three parts include the introduction, factors in early American medical education, and the evolution of the American system of medical education.

Wartime standards of publication have been conformed to, but the type is clear and easily read. There are no illustrations. The bibliography is extensive and is divided into the following sections: general work; journals, newspapers and society proceedings; and manuscripts, but does not include the college catalogues since reference is made to these in the text. To facilitate reference, there is a general index and an index of personal names.

The author's style is informal and interpretive in which he presents an integrated and delightful picture of a very important century of American medical education from a broad point of view.

Every medical school library should have a copy of this book on its reference shelf. Graduates of the schools described in detail will enjoy the factual and impartial presentation of the history of their respective schools. This work will take its rightful place beside the important histories of other phases of American Medicine, and the author is to be congratulated upon his contribution.

J. E. S.

## BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Essentials of Clinical Allergy.* By SAMUEL J. TAUB, M.D. 198 pages; 23.5 × 15.5 cm. 1945. The Williams & Wilkins Company, Baltimore. Price, \$3.00.

*Plaster of Paris Technique in the Treatment of Fractures and Other Injuries.* By T. B. QUIGLEY, Lt. Col., M.C., A.U.S. 107 pages; 24 × 16 cm. 1945. The Macmillan Company, New York. Price, \$3.50.

*Textbook of Obstetrics.* Stander's 3rd Revision—represents the Ninth Edition of Williams' Obstetrics. By HENRICUS J. STANDER, M.D., F.A.C.S. 1,277 pages; 25 × 17 cm. 1945. D. Appleton-Century Company, New York. Price, \$10.00.

- A Handbook for Dissectors.* 2nd Edition. By J. C. BOILEAU GRANT, Prof. of Anatomy, University of Toronto, and H. A. CATES, Assoc. Prof. of Anatomy, University of Toronto. 390 pages; 19 × 12.5 cm. 1945. The Williams & Wilkins Company, Baltimore. Price, \$2.50.
- Handbook of Physiology and Biochemistry.* By R. J. S. McDOWALL, M.D., D.Sc., M.R.C.P. 898 pages; 21 × 15 cm. 1945. The Blakiston Company, Philadelphia. Price, \$6.00.
- Recent Advances in Neurology and Neuropsychiatry.* 5th Edition. By W. RUSSELL BRAIN, M.A., D.M. (Oxon.), F.R.C.P., and E. B. STRAUSS, M.A., D.M. (Oxon.), F.R.C.P. 363 pages; 21 × 14 cm. 1945. The Blakiston Company, Philadelphia. Price, \$5.00.
- How a Baby Grows.* By ARNOLD GESELL, Ph.D., M.D. 78 pages; 30.5 × 24 cm. 1945. Harper & Brothers, New York. Price, \$2.00.
- What People Are. A Study of Normal Young Men.* By CLARK W. HEATH. In Collaboration with LUCIEN BROUHA, LEWIS W. GREGORY, CARL C. SELTZER, FREDERIC L. WELLS, and WILLIAM L. WOODS—The Grant Study, Department of Hygiene, Harvard University. Preface by ARLIE V. BOCK. 141 pages; 21.5 × 14.5 cm. 1945. Harvard University Press, Cambridge, Massachusetts. Price, \$2.00.
- Pulmonary Tuberculosis. A Handbook for Students and Practitioners.* By R. Y. KEERS, M.D. (Edin.), F.R.F.P.S. (Glas.), and B. G. RIGDEN, M.R.C.S. (Eng.), L.R.C.P. (Lond.). With a Foreword by F. H. YOUNG, O.B.E., M.D. (Camb.), F.R.C.P. (Lond.), D.P.H. 273 pages; 19 × 12.5 cm. 1945. The Williams & Wilkins Company, Baltimore. Price, \$5.00.
- A Text-Book of Pharmacognosy.* Fourth Edition. By GEORGE EDWARD TREASE, B.Pharm., Ph.C., F.R.I.C., F.L.S. Revised with the Assistance of H. E. STREET, B.Sc., Ph.D., Ph.C., and E. O'F. WALSH, B.Sc., A.R.I.C., Ph.C. With Contributions by R. BIENFANG, B.S., M.S., Ph.D., H. M. HIRST, M.P.S., F.R.H.S., H. O. MEEK, Ph.C., and A. H. WARE, Ph.C. 799 pages; 22 × 15 cm. 1945. The Williams & Wilkins Company, Baltimore. Price, \$7.50.

## COLLEGE NEWS NOTES

### DR. CHRISTOPHER C. SHAW, F.A.C.P., APPOINTED EDUCATIONAL DIRECTOR, AMERICAN COLLEGE OF PHYSICIANS

Dr. Christopher C. Shaw, F.A.C.P., formerly of Bellows Falls, Vermont, has been appointed, as of November 1, 1945, the Educational Director of the American College of Physicians, in accordance with resolutions of the Board of Regents, June 10, 1945, providing for the establishment of this post. Dr. Shaw, under the Executive Secretary of the College, has immediately taken over the direction of the postgraduate courses, research fellowships, clinical fellowships, program for the aid of members returning from the Armed Services, and other educational features in the College program.

Dr. Shaw was born in Chichester, New York; attended St. Paul's School at Concord, New Hampshire; Yale University (Ph.B., 1924), and graduated from the University of Maryland School of Medicine, Baltimore, in 1931. He is a diplomate of the National Board of Medical Examiners and of the American Board of Internal Medicine. He did postgraduate work at Johns Hopkins University, the University of Maryland, and the Harvard Medical School, the latter under a Commonwealth Fund Fellowship. His teaching experience includes appointments in his earlier career at St. Paul's School, the University of Maryland School of Medicine, Johns Hopkins University School of Medicine, and the University of Vermont College of Medicine. His internship was spent at the University of Maryland Hospital, and he served one year as a resident at the Baltimore City Hospital, and eighteen months with the Metropolitan Life Insurance Company Sanatorium at Mt. McGregor, New York. He was engaged in the practice of internal medicine at Bellows Falls, Vermont, and was pathologist at the Rockingham General Hospital there. He has published a number of articles in well recognized medical journals. He was at one time Secretary of the Medical Staff of the Rockingham Hospital Association, President of the Windham County Medical Society, and member of the House of Delegates of the Vermont State Medical Society. He is a Fellow of the American Medical Association, and has been a Fellow of the American College of Physicians since 1940. Early in the war he volunteered for active service in the Medical Corps of the U. S. Navy, and rose rapidly through the ranks of Lieutenant Commander, Commander, and Captain. He graduated from the Naval School of Aviation Medicine at Pensacola and served thereafter on its faculty, was designated a Flight Surgeon by the Bureau of Aeronautics of the Navy Department, and served as Senior Medical Officer at the U. S. Naval Auxiliary Air Station, Whiting Field, Milton, Florida. He later served as Senior Medical Officer and Flight Surgeon of the Aircraft Carrier U. S. S. Solomons, and served in the combat zones of both the Atlantic and the Pacific. Upon his separation from active duty in the Navy, he was appointed to this important post as Educational Director of the College.

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### NEW LIFE MEMBERS OF THE COLLEGE

The announcement of the following new Life Members of the College is made with gratification:

- Dr. Samuel L. Crow, F.A.C.P., Asheville, N. C.
- Dr. James F. Anderson, F.A.C.P., Los Angeles, Calif.
- Dr. Alexander S. Wiener, F.A.C.P., Brooklyn, N. Y.
- Dr. Theodore L. Squier, F.A.C.P., Milwaukee, Wis.
- Dr. Frank W. Otto, F.A.C.P., Los Angeles, Calif.

Before January 1, 1946, is the most propitious time for Fellows to take out Life Membership. Such fees are deductible on Federal income taxes which are undoubtedly at their peak. It is anticipated that there will be some reduction in the income tax rate for 1946, thus allowing a smaller deduction for such fees. Many Fellows of the College are at present paying between 25 and 45 per cent of their income to Federal taxes. Obviously, the saving on the Life Membership fee is higher at the present time than may be anticipated in the future.

#### A.C.P. MEMBERS IN THE ARMED FORCES

Up to the time of the release of this news item, 1,928 Fellows and Associates of the American College of Physicians have served on active military duty during World War II. One not previously recorded was Dr. Eugene F. DuBois, F.A.C.P., New York City, who served in the Medical Corps of the U. S. Naval Reserve intermittently between October 15, 1942, and April 5, 1945.

The number of retirements from active duty is rapidly growing. Since the last publication of this journal the following members of the College have been reported retired or on terminal leave:

Frank M. Acree, Greenville, Miss. (Capt., MC, AUS), F.A.C.P.  
 Walter P. Adams, Norfolk, Va. (Lt. Comdr., MC, USNR), F.A.C.P.  
 William H. Allen, Washington, D. C. (Col., MC, USA), F.A.C.P.  
 Frank J. Altschul, Long Branch, N. J. (Major, MC, AUS), F.A.C.P.  
 Irving L. Applebaum, Newark, N. J. (Major, MC, AUS), F.A.C.P.  
 Theodore L. Badger, Boston, Mass. (Lt. Col., MC, AUS), F.A.C.P.  
 Robert S. Baldwin, formerly Marshfield, Wis., now Highland Park, Ill. (Lt. Col., MC, AUS, (Associate)  
 Glenn L. Barnum, Pasadena, Calif. (Lt. Comdr., MC, USNR), (Associate)  
 Clifton H. Berlinghof, Binghamton, N. Y. (Lt. Col., MC, AUS), F.A.C.P.  
 Michael Bevilacqua, Woodhaven, L. I., N. Y. (Major, MC, AUS), F.A.C.P.  
 Staige D. Blackford, Charlottesville, Va. (Lt. Col., MC, AUS), F.A.C.P.  
 Elton R. Blaisdell, Portland, Maine (Lt. Col., MC, AUS), F.A.C.P.  
 Rankin C. Blount, Lexington, Ky. (Major, MC, AUS), F.A.C.P.  
 Louis H. Charney, Oklahoma City, Okla. (Major, MC, AUS), F.A.C.P.  
 A. Henry Clagett, Jr., Philadelphia, Pa., and Moorestown, N. J. (Lt. Col., MC, AUS), (Associate)  
 Milton H. Clifford, Cambridge, Mass. (Lt. Col., MC, AUS), F.A.C.P.  
 Darrell C. Crain, Jr., Washington, D. C. (Capt., MC, AUS), (Associate)  
 Casimir J. Czarnecki, Toledo, Ohio (Major, MC, AUS), F.A.C.P.  
 Lester C. Feener, El Paso, Tex. (Major, MC, AUS), (Associate)  
 Ferdinand Fetter, Philadelphia, Pa. (Comdr., MC, USNR), F.A.C.P.  
 Stephen A. Foote, Jr., Houston, Tex. (Major, MC, AUS), F.A.C.P.  
 S. Charles Franco, Brooklyn, N. Y. (Major, MC, AUS), F.A.C.P.  
 Lee Pettit Gay, St. Louis, Mo. (Major, MC, AUS), F.A.C.P.  
 Burgess Lee Gordon, Philadelphia, Pa. (Lt. Col., MC, AUS), F.A.C.P.  
 Joseph M. Hayman, Jr., Cleveland, Ohio (Col., MC, AUS), F.A.C.P.  
 James A. Halsted, Dedham, Mass. (Major, MC, AUS), F.A.C.P.  
 Harold J. Harris, New York, N. Y. (Lt. Comdr., MC, USNR), F.A.C.P.  
 Alf Cornelius Johnson, Great Falls, Mont. (Major, MC, AUS), F.A.C.P.  
 Carl August Johnson, Chicago, Ill. (Major, MC, AUS), (Associate)  
 Clarence E. Johnson, Long Beach, Calif. (Major, MC, AUS), F.A.C.P.  
 Benjamin Juliar, Detroit, Mich. (Major, MC, AUS), F.A.C.P.  
 Max J. Klainer, Stoneham, Mass. (Capt., MC, AUS), (Associate)

Charles Edward Kossmann, New York, N. Y. (Lt. Col., MC, AUS), (Associate)  
 Harry C. Kroon, Syracuse, N. Y. (Major, MC, AUS), F.A.C.P.  
 John W. P. Love, Willow Grove, Pa. (Major, MC, AUS), F.A.C.P.  
 Edgar M. McPeak, San Antonio, Tex. (Major, MC, AUS), F.A.C.P.  
 William S. Middleton, Madison, Wis. (Col., MC, AUS), F.A.C.P.  
 William C. Moloney, Boston, Mass. (Major, MC, AUS), (Associate)  
 Adolph T. Ogaard, New Orleans, La. (Major, MC, AUS), F.A.C.P.  
 Richard Ellsworth Olsen, Pontiac, Mich. (Lt. Comdr., MC, USNR), F.A.C.P.  
 Samuel A. Overstreet, Louisville, Ky. (Lt. Comdr., MC, USNR), F.A.C.P.  
 Emmet F. Pearson, Springfield, Ill. (Lt. Col., MC, AUS), F.A.C.P.  
 Frank S. Perkin, Detroit, Mich. (Major, MC, AUS), F.A.C.P.  
 Elbert L. Persons, Durham, N. C. (Lt. Col., MC, AUS), F.A.C.P.  
 Stephen Reynolds, Santa Barbara, Calif. (Major, MC, AUS), (Associate)  
 Nelson G. Russell, Jr., Buffalo, N. Y. (Major, MC, AUS), F.A.C.P.  
 Christopher C. Shaw, Philadelphia, Pa. (Capt., MC, USNR), F.A.C.P.  
 Hugh P. Smith, Greenville, S. C. (Lt. Col., MC, AUS), F.A.C.P.  
 William Stein, New Brunswick, N. J. (Major, MC, AUS) (Associate)  
 Stuart R. Townsend, Montreal, Que., Can. (Wing Comdr., RCAF), (Associate)  
 Paul R. Wilner, Washington, D. C. (Major, MC, AUS), (Associate)  
 Edward E. Woldman, Cleveland Heights, Ohio (Lt. Col., MC, AUS), F.A.C.P.

Some of these discharges are of a considerably passed date but have only now been reported. Members are urged to notify the Executive Offices, 4200 Pine Street, Philadelphia 4, Pa., promptly of their retirements, giving dates and changes of address.

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#### CHANGES OF ADDRESS

Members of the College and subscribers to the ANNALS OF INTERNAL MEDICINE are urged to keep the Executive Offices of the College informed of all changes of address. Numerous copies of the journal are returned because members and subscribers have failed to notify the College of their change of location. This is largely applicable to those on military duty.

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#### PUBLICATION OF THE A.C.P. MEMBERSHIP ROSTER POSTPONED

The sudden end of the war rendered valueless biographical data collected from members in the case of its more than 1,900 members on active military duty, and likewise affected the activities of many civilian members connected with war activities. Furthermore, the addresses of the great majority of members on military duty have been rapidly changing, and it has been found impractical to publish either a new Roster or a Supplement to the 1943 Roster at this time. It is planned, however, to publish a complete Directory during 1946.

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#### EXAMINATIONS, AMERICAN BOARD OF INTERNAL MEDICINE

The oral examination scheduled by this Board at San Francisco on October 15, 16, 17 had to be cancelled owing to the fact that no hotel accommodations could be obtained either for the Board or for the candidates.

The next written examination is scheduled for February 18, 1946, in various cities, applications to be filed by December 1, 1945, with William A. Werrell, M.D., Assistant Secretary-Treasurer, 1 West Main Street, Madison 3, Wisconsin.

## GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College library of publications by members are gratefully acknowledged:

- Major Lewis Barbato, (MC), AUS, Associate, Denver, Colo.—1 reprint, "The State Mental Hospital—An Educational Center."  
 Dr. Benjamin M. Bernstein, F.A.C.P., Brooklyn, N. Y.—1 reprint, "Neuro-Functional Spasm."  
 Lt. Comdr. Albert H. Douglas, (MC), USNR, F.A.C.P., New River, N. C.—2 reprints, "Penicillin in Malignant Granulocytopenia" and "Mechanism of T Deflection in the Precordial Electrocardiogram."  
 Lt. Comdr. Adolph M. Hutter, (MC), USNR, F.A.C.P., San Francisco, Calif.—1 reprint, "The Transmission of Penicillin through the Placenta."  
 Dr. Arthur H. Jackson, F.A.C.P., Waterbury, Conn.—1 reprint, "Electric Shock Therapy: Its Use in a General Hospital."  
 Comdr. M. J. Matzner, (MC), USNR, F.A.C.P., Brooklyn, N. Y.—2 reprints, "Postvaccinal (Yellow Fever) Jaundice" and "An Optical Fluorescence Comparator."

Acknowledgment is also made of the receipt of the *Collected Papers* from the Squibb Institute for Medical Research, New Brunswick, N. J., Volume 3, 1943-44, Dr. George A. Harrop, F.A.C.P., Director.

## REPORT FROM THE OFFICE OF THE SURGEON GENERAL, U. S. ARMY

*Major General George C. Dunham Succeeds Nelson Rockefeller*

Major General George C. Dunham, (MC), USA, F.A.C.P., who has served in the Army Medical Corps since 1916, has submitted his resignation as President of the Institute of Inter-American Affairs and Deputy Director of the Office of Inter-American Affairs, owing to reasons of health. General Dunham will succeed Nelson A. Rockefeller as Chairman of the Board of Directors of the Institute.

The General's book, "Military Preventive Medicine," has become a standard text. His fame as the "flying doctor of the Americas" is evidence of his average of 100,000 miles of airplane travel to visit more than 1,000 health, sanitation and food projects organized under his direction. For this contribution to inter-American relations, General Dunham was awarded the Distinguished Service Medal with a presidential citation in the early part of August. He also received national honors from the governments of Brazil, Bolivia, Nicaragua, Chile, Haiti, and Peru.

*Lieutenant Colonel Staige D. Blackford Returns to University of Virginia*

Lt. Col. Staige D. Blackford, (MC), F.A.C.P., who served thirty months in Italy and North Africa as Chief of the Medical Service of the 8th Evacuation Hospital and for the past two months as Chief of the Medical Service at Valley Forge General Hospital, has recently returned to his civilian position of Associate Professor of Internal Medicine in the Department of Medicine at the University of Virginia. A resident of Virginia, Colonel Blackford served in World War I and was presented the Croix de Guerre by the French government.

*Promotion, Medical Corps*

Howard Avery Lindberg, F.A.C.P., Chicago, Ill., has been advanced from Major to Lieutenant Colonel.

*Surgeon General Urges Prompt Release of Eligible Personnel*

Major General Norman T. Kirk, F.A.C.P., the Surgeon General of the Army, has expressed the desire that all commanding officers give the fullest possible co-operation towards effecting the early release of Medical Department personnel who are eligible for separation from the service under the announced policy.

At the same time he urged that all Medical Department personnel who occupy key positions and who are eligible for separation under the present criteria volunteer to continue on active duty to assist in maintaining the present high standards of medical care if no replacement is immediately available. It is contemplated that a period of six months' duty will be sufficient time to allow for the arrival of a replacement or for training an officer to take over duties of key positions and thus allow all officers eligible for release to be returned to civilian life.

General Kirk requested that commanding officers make every effort to obtain replacements for Medical Department personnel eligible for release in order that those officers might be returned to civil life at the earliest possible moment.

Under the announced Medical Department demobilization policy, Medical and Dental Corps officers are eligible for release provided they meet any one of the following criteria:

- a. Adjusted service score of 80 or above.
- b. 48 years of age to the nearest birthday or above.
- c. Entry on active duty prior to Pearl Harbor excepting critical specialists qualified in eye, ear, nose and throat, plastic surgery, orthopedic surgery, neuropsychiatry or laboratory clinicians. Officers qualified in these specialties are eligible for release if they entered on active duty prior to January 1, 1941, or if they meet the criteria on points or age.

This revised policy on separation is expected to return 13,000 physicians, 3,500 dentists, 25,000 nurses and a large number of other Medical Department officers to civilian life by the first of the year.

It will be necessary to retain a large number of low score men in the service for replacement for overseas men having high ASR scores. Other low score men must of necessity be retained in the service to carry on the necessary activities of the Medical Department in this country and in theaters where American troops are operating.

It is intended that no one eligible for release will be held in the Army because there are men with higher scores overseas who have not been returned home. Eligible men will be discharged as rapidly as they can be processed for separation.

No enlisted personnel with a sufficient number of critical points will be kept because of "military necessity" except those very few men classified in one of three essential technical skills. These are: Orthopedic mechanics, electro-encephalographers who operate electrocardiac equipment and radio transmitter attendants. The latter is not in the Medical Department.

*Total Streptomycin Production Only Fourteen Ounces a Month*

The War Department said recently that streptomycin, the new wonder sister drug to penicillin, was being used in thirty Army general hospitals over the country, but that it was so difficult to obtain that the total output of the four companies now making it has been only fourteen ounces a month.

The Army is receiving many requests for the drug for use in treatment of urinary and other infections caused by gram-negative bacteria which do not respond to penicillin, but these cannot be met since the Army neither controls the supply nor can get enough for its own needs in treatment of battle-wounded soldiers.

General Kirk said that the four companies, Merck, Upjohn, Abbott and Squibb,

were the principal manufacturers of the new product, but that other concerns were working at experimental production at pilot plants and that any civilian request for streptomycin naturally would go to these companies.

A gram, or 1,000,000 units, is the standard daily dose administered in three injections over a twenty-four hour period.

Production is limited severely because the drug is obtained from a natural fungus found in the soil and must be grown under carefully controlled laboratory conditions which cannot be hurried.

The phenomenal production of penicillin which brought it from a laboratory curiosity to a commonly-used drug and the price from astronomical figures to about a dollar a dose was due in part to pressure of wartime needs.

The Surgeon General explained that the Army's principal needs are for treatment of soldiers with severed spinal cords who develop urinary tract infections because of a loss of bladder function, and to some extent in treating some cases of meningitis and other infections which do not respond readily to penicillin therapy.

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#### MEMBERS INVITED TO REPORT OPENINGS FOR DOCTORS TO THE COLLEGE

Members of the College will perform a service by reporting to the Educational Director of the College, Dr. Christopher C. Shaw, 4200 Pine Street, Philadelphia 4, Pa., openings that might be filled by Associates and Fellows returning to civilian life from military service. There are a number of College members well qualified for teaching in the various fields of internal medicine, for residencies, and for private or group practice. The Educational Director's office will be pleased to act as a medium of contact. The College program calls for an active and effective service to its members returning to civilian life.

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Dr. Wallace M. Yater, for many years Professor of Medicine at Georgetown University School of Medicine, Washington, D. C., has resigned that post as of October 27, 1945.

Dr. Yater received his A.B. degree from George Washington University, his M.D. degree from Georgetown, and his Master of Science degree from the Mayo Foundation of the University of Minnesota. He has been a Fellow of the College and its Governor for the District of Columbia for several years. He has devoted twenty-one years to the field of medical education, and has been head of the Department of Medicine at the Gallinger Municipal Hospital for thirteen years. He is a diplomate of the American Board of Internal Medicine, with special certification in cardiovascular disease. He is Past Chairman of the Section on Experimental Medicine and Therapeutics of the American Medical Association; Past Chairman, Section for the Study of the Peripheral Circulation, American Medical Association; member, Committee on Medicine, National Research Council, and member of its Subcommittee on Cardiovascular Diseases; member, American Society for Clinical Investigation; Director, American Heart Association; member, Sigma Xi; Editor, Medical Annals of the District of Columbia; author of approximately 150 published articles on medical subjects (mainly original contributions to medical science) and 2 medical textbooks; deliverer of a Kober Memorial Lecture, a Mayo Foundation Lecture, and many medical addresses the country over. During his tenure as Associate Professor of Medicine and Professor of Medicine, he has trained approximately forty-five Fellows in Medicine as well as directed the Department of Medicine.

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Dr. Frank H. Krusen, F.A.C.P., Director of the Baruch Committee on Physical Medicine, has announced the appointment of Colonel Howard A. Rusk, F.A.C.P., (MC), AUS, formerly of St. Louis, as Consultant on Physical Rehabilitation for the

Baruch Committee. Colonel Rusk, whose pioneering work as Chief of the Convalescent Division of the Air Surgeon has attracted national attention, will make his headquarters at the New York office of the Committee created a year ago by Bernard M. Baruch.

Colonel Rusk has resigned from the Army to serve the Committee temporarily in endeavoring to apply his Army experience in physical rehabilitation to the urgent civilian needs in this phase of physical medicine.

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Dr. Milford Leroy Hobbs, F.A.C.P., formerly of Burlington, Vermont, last July 1 became Pathologist and Director of the Laboratory of the Fairmont General Hospital at Fairmont, West Virginia.

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Dr. William Herschel Allen, F.A.C.P., has retired from the Medical Corps of the Regular U. S. Army, effective September 30, 1945, and has entered the practice of internal medicine on the staff of the Santa Barbara Clinic at Santa Barbara, California.

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#### A. C. P. POSTGRADUATE COURSES, AUTUMN SCHEDULE

The entire group of seven courses scheduled between October 8 and December 1, 1945, have been oversubscribed in every instance. Never before has the demand for these courses been so great. The College was able to accommodate but a small percentage of non-members in the courses but a special effort was made to accommodate as many as possible of the medical officers recently separated or soon to be separated from the military services.

The College is preparing an extended schedule of courses for the spring of 1946. The Educational Director will appreciate receiving suggestions of courses most desired, and he will attempt to arrange them where possible.

For the information of members of the College and readers of this journal, we publish hereafter the outline of the course in Advanced Cardiology given at the Philadelphia General Hospital, November 26-December 1, since it was not previously published in these pages.

#### COURSE No. 7—ADVANCED CARDIOLOGY

(November 26-December 1, 1945)

*Philadelphia General Hospital, Philadelphia, Pa.*

THOMAS M. McMILLAN, M.D., F.A.C.P., *Director*

#### *Officers of Instruction*

Oscar V. Batson, M.D., Professor of Anatomy, University of Pennsylvania Graduate School of Medicine.

Samuel Bellet, M.D., F.A.C.P., Associate in Cardiology, University of Pennsylvania Graduate School of Medicine; Assistant Chief, Cardiology, Philadelphia General Hospital.

Henry L. Bockus, M.D., F.A.C.P., Professor of Gastroenterology, University of Pennsylvania Graduate School of Medicine.

W. Edward Chamberlain, M.D., F.A.C.P., Professor of Radiology, Temple University School of Medicine.

Julius Comroe, Jr., M.D., F.A.C.P., Assistant Professor of Pharmacology, University of Pennsylvania School of Medicine.

William Dock, M.D., F.A.C.P., Professor of Medicine, Long Island College of Medicine, New York, N. Y.

- Robert Dripps, M.D., Assistant Professor of Anesthesiology and Associate in Pharmacology, University of Pennsylvania School of Medicine.
- Thomas M. Durant, M.D., F.A.C.P., Associate Professor of Internal Medicine, Temple University School of Medicine.
- Mary H. Easby, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Woman's Medical College of Pennsylvania; President, Philadelphia Heart Association.
- Harrison F. Flippin, M.D., F.A.C.P., Assistant Professor of Medicine, University of Pennsylvania Graduate School of Medicine.
- Harry Gold, M.D., Associate Professor of Pharmacology, Cornell University Medical College, New York, N. Y.
- Benjamin Gouley, M.D., Chief Coroner's Physician, City of Philadelphia.
- John Q. Griffith, Jr., M.D., F.A.C.P., Associate in Medicine and A. Atwater Kent Fellow in Medicine, University of Pennsylvania School of Medicine.
- Seymour Kety, M.D., Associate in Pharmacology, University of Pennsylvania School of Medicine.
- David W. Kramer, M.D., F.A.C.P., Assistant Professor of Medicine, Jefferson Medical College of Philadelphia.
- William G. Leaman, Jr., M.D., F.A.C.P., Professor of Medicine, Woman's Medical College of Pennsylvania.
- Alexander Margolies, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine.
- Thomas M. McMillan, M.D., F.A.C.P., Associate Professor of Cardiology, University of Pennsylvania Graduate School of Medicine; Chief, Cardiology, Philadelphia General Hospital.
- Herman Ostrum, M.D., Radiologist, Philadelphia General Hospital; Assistant Professor of Radiology, University of Pennsylvania Graduate School of Medicine.
- Rufus S. Reeves, M.D., F.A.C.P., Director, Department of Public Health of Philadelphia.
- Major George P. Robb, (MC), AUS, F.A.C.P., Walter Reed General Hospital, Washington, D. C.; Assistant Medical Director, Metropolitan Life Insurance Company, New York.
- Ella Roberts, M.D., F.A.C.P., Medical Director, Children's Heart Hospital of Philadelphia.
- Hugo Roesler, M.D., F.A.C.P., Assistant Professor of Radiology, Temple University School of Medicine; Cardiologist, Department of Medicine, Temple University Hospital.
- Isaac Starr, M.D., Milton Bixler Hartzell Research Professor of Therapeutics, University of Pennsylvania School of Medicine.
- William D. Stroud, M.D., F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine.
- Helen Taussig, M.D., Pediatrician, Johns Hopkins Hospital; Associate in Pediatrics, Johns Hopkins University School of Medicine; Baltimore, Md.
- Edward Weiss, M.D., F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine.
- Charles C. Wolferth, M.D., F.A.C.P., Professor of Clinical Medicine, University of Pennsylvania School of Medicine.

#### *Outline of Course*

*Monday, November 26.*

A.M. Session

9:15- 9:30 Registration.

9:30- 9:45 Welcome and Announcements.

Dr. Rufus S. Reeves, Director, Department of Public Health of Philadelphia.

- 9:45-10:45 Some of the Newer Conceptions of Congestive Heart Failure.  
Dr. Starr.
- 10:45-11:00 Recess.
- 11:00-12:00 The Physiology, the Diagnosis and the Treatment of the More  
Important Congenital Malformations of the Heart.  
Dr. Taussig.
- 12:00- 2:00 Recess.
- P.M. Session
- 2:00- 3:00 The Principles underlying Electrocardiography.  
Dr. Wolferth.
- 3:00- 4:00 The Physiology, the Diagnosis and the Treatment of the More  
Important Congenital Malformations of the Heart (con-  
cluded).  
Dr. Taussig.
- 4:00- 4:10 Recess.
- 4:10- 4:45 Air Embolism: Some of Its Effects upon the Heart and Its Treat-  
ment.  
Dr. Durant.
- 5:00 Cocktail Party.  
Headquarters, American College of Physicians, 4200 Pine  
Street.

*Tuesday, November 27.*

- A.M. Session
- 9:00-10:00 Acute Pericarditis.  
Dr. McMillan.
- 10:00-10:45 Roentgen Findings in Pericarditis.  
Dr. Ostrum.
- 10:45-11:00 Recess.
- 11:00-12:00 Heart Sounds.  
Dr. Margolies.
- 12:00- 2:00 Recess.
- P.M. Session
- 2:00- 3:00 Roentgen Findings in the Lungs in Heart Disease.  
Dr. Roesler.
- 3:00- 4:00 Oxygen in the Treatment of Circulatory Disease.  
Dr. Comroe.
- 4:00- 4:10 Recess.
- 4:10- 5:00 Syncope of Cardiac Origin.  
Dr. Bellet.

*Wednesday, November 28.*

- A.M. Session
- 9:00- 9:30 The Importance and the Public Health Aspects of Rheumatic Fever.  
Dr. Stroud.
- 9:30-10:00 The Use of the Sulpha Drugs in Rheumatic Fever.  
Dr. Roberts.
- 10:00-10:50 The Psychosomatic Aspects of Cardiovascular Disease.  
Dr. Weiss.
- 10:50-11:00 Recess.
- 11:00-12:00 The Principles Underlying Electrocardiography (continued).  
Dr. Wolferth.
- 12:00- 2:00 Recess.

## P.M. Session

- 2:00- 2:55 Some of the Newer Methods of Studying the Circulation.  
Dr. Kety.  
2:55- 3:55 Predilection of Atherosclerosis for the Coronary Arteries.  
Dr. Dock.  
3:55- 4:05 Recess.  
4:05- 5:00 The Effects of Drugs upon the Heart.  
Dr. Starr.

*Thursday, November 29.*

## A.M. Session

- 9:00-10:00 Electrocardiography. Brief Considerations of  
(1) The Use of Large Doses of Quinidine in the Treatment of Ventricular Paroxysmal Tachycardia Following Myocardial Infarction.  
(2) Electrocardiographic Patterns Simulating Myocardial Infarction.  
(3) Dissecting Aneurysm Rupturing into the Pericardium.  
Dr. McMillan and Dr. Bellet.  
10:00-10:45 Some of the Causes of Sudden Death as Seen by a Coroner's Physician.  
Dr. Gouley.  
10:45-11:00 Recess.  
11:00-12:00 Cardioangiography.  
Major Robb.  
12:00- 2:00 Recess.  
P.M. Session  
2:00- 3:00 Digitalis and Some of the Newer Glycosides.  
Dr. Gold.  
3:00- 3:55 A New Roentgen Method of Determining the Amplitude of Cardiac Contraction.  
Dr. Chamberlain.  
3:55- 4:05 Recess.  
4:05- 5:00 The Heart and Anesthesia.  
Dr. Dripps.

*Friday, November 30.*

## A.M. Session

- 9:00- 9:55 The Medical Treatment of Hypertension.  
Dr. Griffith.  
9:55-10:55 The Principles Underlying Electrocardiography (concluded).  
Dr. Wolferth.  
10:55-11:05 Recess.  
11:05-12:00 Heart Sounds (concluded).  
Dr. Margolies.  
12:00- 2:00 Recess.  
P.M. Session  
2:00- 3:00 The Ballistocardiograph as a Clinical Instrument.  
Dr. Starr.  
3:00- 3:50 Some of the Important Features of Cardiac Anatomy.  
Dr. Batson.  
3:50- 4:00 Recess.

4:00- 5:00 Question and Answer Period.

Dr. Leaman, Leader; Drs. Bellet, Durant, Easby, Kramer, Margolies, McMillan, Roesler, Stroud and Wolferth.

*Saturday, December 1.*

9:00-10:00 (1) A Critical Consideration of the Roentgen Methods of Determining Heart Size.

(2) Roentgen Findings in Disease of the Aorta.

Dr. Roesler.

10:00-10:50 Results of the Newer Treatment of Bacterial Endocarditis.

Dr. Flippin.

10:50-11:00 Recess.

11:00-12:00 The Relationship of Cardiovascular and Gastrointestinal Symptoms.

Dr. Bockus.

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Lieutenant Colonel James E. Cottrell (MC), F.A.C.P., was recently made Chief of Medical Service at the Lovell General Hospital, Fort Devens, Massachusetts, succeeding Colonel Julien E. Benjamin, F.A.C.P., who has been separated from the Army and returned to Cincinnati. It is anticipated that Colonel Cottrell may also be separated from the service in the near future and will return to the practice of Internal Medicine in Philadelphia.

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Captain Richard A. Kern, F.A.C.P., Philadelphia, Chief of Medicine at the Philadelphia Naval Hospital, was recently promoted from Captain to the rank of Commodore.

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Dr. Maynard E. Holmes, F.A.C.P., Professor of Clinical Medicine at Syracuse University College of Medicine, gave a graduate lecture before the Broome County Medical Society at Binghamton, N. Y., on October 9, 1945, on "The Management of Diabetes with the Newer Forms of Insulin." The meeting was arranged by the Committee on Public Health and Education of the New York State Medical Society.

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Mead Johnson and Company, Evansville, Indiana, publishes annually a catalogue of medical books published during the year, their last edition being "Medical Books Published During 1944." This publication has been especially timely and valuable during the war years, particularly among countries in Europe where they have been cut off from contact with the publication of medical books in the United States. This publication also is valuable to returning medical officers from the armed forces and of interest to many civilian physicians.

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#### DR. POTTENGER MARKS THREE ANNIVERSARIES AT MONROVIA

Dr. Frank M. Pottenger, F.A.C.P., founder of the Pottenger Sanitarium at Monrovia, celebrated on September 27 a three-way anniversary—his 42nd anniversary of the founding of the sanitarium, his 50th anniversary of his going to California to practice medicine, and his 76th birthday. Dr. Pottenger is a past President of the American College of Physicians and has been an active Fellow practically from its conception. He is just completing a new book on "Clinical Tuberculosis."

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Dr. Stuart R. Townsend (Associate) has retired as Wing Commander, Royal Canadian Air Force, and has returned to the faculty of McGill University and to the Attending Staff of the Montreal General Hospital.

Dr. Harold J. Harris, F.A.C.P., has been retired from active naval service and has returned to his offices at Westport, Essex County, New York. Much of his time will be devoted to clinical research in brucellosis in New York.

During November he delivered a series of lectures on brucellosis at the University of Cordoba, Argentina.

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Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, was recently granted the Supreme Decoration of the Order of Merit of Juan Pablo Duarte, grade of Knight Commander, Dominican Republic, "for distinguished service in public office as Director of a noteworthy and alert Department of Health and as a civic statesman in the field of foreign affairs."

Juan Pablo Duarte, the patriot after whom this decoration is named, in 1844 overwhelmed the enemies of his country and with others established the Dominican Republic.

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#### PHYSICIAN-ARTISTS' PRIZE CONTEST

The American Physicians Art Association, with the coöperation of Mead Johnson & Company, is offering an important series of War (Savings) Bonds as prizes to physicians in the armed services and also physicians in civilian practice for their best artistic works depicting the medical profession's "skill and courage and devotion beyond the call of duty."

For full details, write to the Association's Secretary, Dr. F. H. Redewill, Flood Bldg., San Francisco, Calif., or Mead Johnson & Co., Evansville 21, Ind. Also pass this information on to your physician-artist friends, both civilian and military.

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The New York Academy of Medicine is conducting its 20th series of Friday afternoon lectures, held at the Academy, 4:30 o'clock. Among speakers and their subjects are the following: December 7—Senescence of the myocardium—presbycardia—William Dock, F.A.C.P., Professor of Medicine, Long Island College of Medicine; December 14—The therapeutic and toxic actions of some drugs recently introduced in the treatment of cardiac disorders—Arthur C. DeGraff, F.A.C.P., Samuel A. Brown Professor of Therapeutics, New York University College of Medicine; January 4—Current views of rheumatic diseases and their management—Richard H. Freyberg, F.A.C.P., Associate Professor of Clinical Medicine, Cornell University Medical College; Director of Department of Internal Medicine, Hospital for Special Surgery; January 18—Apical systolic murmurs in incipient rheumatic heart disease—Captain Arthur M. Master (MC), USNR, F.A.C.P., Cardiologist, U. S. N. H., St. Albans, Long Island.

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Dr. Hobart A. Reimann, Professor of Medicine, Jefferson Medical College, Philadelphia, has just returned from a 2 months' expedition to Chungking, China, as a member of a team to aid in the control of an epidemic of cholera. The project was sponsored by the United Nations Relief and Rehabilitation Administration at the request of the U. S. Army and the Chinese National Government.

There were 9 members of the Commission, 1 clinician, 1 bacteriologist, several public health experts and sanitary engineers. The Commission arrived in Chungking late in July after the peak of the epidemic had passed. About 2,500 cases were registered but many more undetected ones occurred.

## WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr. B. P. Widmann, Chairman; Dr. J. S. Rodman, Dr. S. P. Reimann.

*U. S. Naval Hospital, Philadelphia, Pennsylvania:*

December 7—Emotional Factors in Physical Illness—Dr. Earl D. Bond.

December 28—Difficulties in the Diagnosis of Surgical Lesions of the Upper Urinary Tract—Dr. Leon Herman.

REGION No. 23 (Nevada, Northern California)—Dr. S. R. Mettier, Chairman; Dr. E. H. Falconer, Dr. D. N. Richards.

*Station Hospital, Camp Stoneman, Pittsburg, California:*

November 17—Plastic Surgery—Dr. George Pierce.

December 15—Diagnosis and Treatment of Abnormal Mechanisms of the Heart—Dr. William J. Kerr.

*Hammond General Hospital, Modesto, California:*

November 21—The Use of Penicillin in Injuries and Infections—Dr. Horace J. McCorkle.

*ASF Regional Station Hospital, Oakland, California:*

December 12—Nephritis—Dr. Thomas Addis.

*Station Hospital, Fort Ord, California:*

November 17—Diseases of the Thyroid: Clinical Diagnosis and Management—Dr. Mayo H. Soley.

December 15—Diseases of the Lungs and Their Treatment—Dr. Philip H. Pierson.

*U. S. Naval Hospital, Treasure Island, California:*

November 16—Interpretation and Misinterpretation of Certain Laboratory Tests—Dr. James Hopper.

December 7—Diagnosis of Atypical Anemias—Dr. Stacy R. Mettier.

*Station Hospital, Camp Roberts, California:*

December 8—Diseases of the Thyroid: Clinical Considerations—Dr. Mayo H. Soley.

*Station Hospital, Chico Army Air Base, Chico, California:*

December 6—Laboratory Aids in the Diagnosis of Disease—Dr. Jesse L. Carr.

*Station Hospital, Stockton Air Field, Stockton, California:*

December 12—The Fundamentals of Endocrine Diagnosis—Major Roberto F. Escamilla.

REGION No. 24 (Southern California)—Lt. Comdr. G. C. Griffith, Chairman; Capt. H. P. Schenck, Dr. J. Churchill, Dr. W. Morrison, Maj. N. Nixon.

*Birmingham General Hospital, Van Nuys, California:*

November 28—Thoracic Surgery—Captain W. L. Rogers.

December 12—Recent Developments in Diabetes—Dr. Howard F. West.

December 26—Neuro-Surgery—Captain Everett Dickinson.

*ASF Regional Hospital, Camp Haan, California:*

December 4—Reconstruction Problems—Captain Fraser L. MacPherson.

*AAF Regional Station Hospital, March Field, California:*

November 20—Compound Fractures—Commander P. E. McMasters.  
December 18—Acute Nephritis—Dr. Lyttle.

*Station Hospital, Camp Cooke, California (afternoon session) and Hoff  
General Hospital, Santa Barbara, California (evening session):*

November 21—Pericarditis—Lieutenant C. Sylvester McGinn.  
December 5—The Cancer Problem in Service Personnel—Lieutenant J. S. Binkley.  
December 19—Problems in Tuberculosis—Commanders W. L. Rogers and A. W. Hobby.

*Torney General Hospital, Palm Springs, California:*

November 20—Peptic Ulcer—Dr. William Boeck.  
December 4—The Rh Factor—Captain George Macer.  
December 18—Hemolytic Streptococcal Respiratory Infections and Their Sequelae—  
Dr. Robert E. Solley.

*U. S. Naval Hospital, Santa Margarita Ranch, Oceanside, California:*

November 22—Modern Concepts of Leprosy—Dr. Maxmillian Obermayer.  
December 13—Communicable Diseases—Major Norman Nixon.  
December 27—Problems Associated with the Surgery of the Biliary Tract—Captain  
Howard K. Gray.

*U. S. Naval Hospital, Long Beach, California:*

November 21—Liver Disease—Captain John Ruddock.  
December 19—Low Back Pain—Major Samuel Weaver.

*U. S. Naval Hospital, Corona, California:*

November 22—Tumor Pathology—Dr. Edward Butt.  
December 13—The Streptococcal Problem—Lieutenant Commander George R. Underwood.  
December 27—The Use of Products of Fibrinogen and Thrombin in Otolaryngology  
—Captain Harry P. Schenck.

*U. S. Naval Air Training Station, San Diego, California:*

December 7—Burns—Captain H. T. D. Kirkbaum.  
December 21—The Penicillin Treatment of Syphilis and Gonorrhea—Commander W.  
W. Duemling.

*AAF Regional and Convalescent Hospital, Santa Ana Army Air Base, California:*

November 20—The Use of Products of Fibrinogen and Thrombin in Otolaryngology  
—Captain Harry P. Schenck.  
December 4—Contagious Diseases—Commander R. A. Trombley.  
December 18—Compound Fractures—Commander P. E. McMasters.

*U. S. Naval Hospital, San Diego, California:*

December 6—The Classification and Diagnosis of the Anemias—Dr. A. G. Foord.

*U. S. Regional Hospital, Pasadena, California:*

December 10—The Rh Factor—Captain George Macer.

## FELLOWSHIPS OFFERED BY THE AMERICAN COLLEGE OF PHYSICIANS

*Research Fellowships*

The American College of Physicians has resumed its Research Fellowships in Medicine, which were discontinued during the War. These fellowships, limited in number, are designed to provide an opportunity for research training either in the basic medical sciences, or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory in which he has chosen to work and that the laboratory will supply the facilities necessary for the proper pursuit of the research. The term of appointment is for one year. The fellowship stipend will be from \$1,800.00 to \$2,500.00 per annum.

*Clinical Fellowships*

In order to assist in providing opportunities for postgraduate education in Internal Medicine for medical officers discharged from the Armed Forces, the American College of Physicians has established a limited number of Clinical Fellowships in Medicine for 1946. These fellowships are available for physicians honorably discharged from the Armed Forces who are Fellows, Associates or prospective candidates for Associateship in the College. They are designed to provide opportunity for advanced clinical training in Internal Medicine, or in any of its special fields. They are limited to a term of one year, may start at any time during 1946, and will not be renewable. Assurance must be provided that the applicant will be acceptable in the clinic in which he has chosen to work. The fellowship stipend will ordinarily be from \$1,800.00 to \$3,000.00, depending on individual circumstances.

Application forms for these fellowships will be supplied on request to the American College of Physicians, 4200 Pine St., Philadelphia 4, Pa. Decision with respect to award of a fellowship will be made and the applicant notified of the action taken as soon as possible after receipt of the application and review by the Committee on Fellowships and Awards.

## SPECIAL NOTICES

## COMMITTEE ON GROWTH OF THE NATIONAL RESEARCH COUNCIL

The appointment of a "Committee on Growth," with membership designed to be broadly representative of the fields concerned in cancer research, both basic and clinical, has already been announced by the National Research Council of the National Academy of Sciences. The Committee was created, within the Division of Medical Sciences of the Council, as a result of action by the American Cancer Society designating the Academy as its scientific advisor for research.

The Committee wishes to call the attention of interested investigators to the general outline of endeavor which it proposes to foster and the general principles by which it will be guided. The Committee accepts the interpretation of its field of interest as including reliance on, contact with and support of research in the basic sciences bearing broadly on the whole phenomenon of growth.

The Committee has adopted the following major principles by which, in so far as possible, it will be guided in its sponsorship of research and training programs:

- (a) Desirability of long-term grants to projects of major importance.
- (b) Grants, where possible, of such magnitude as to permit individual investigators to appoint associates for long-term training periods.
- (c) Granting of fellowships to institutions for training of workers to acquire new technics and wider experience.

- (d) Maintenance of continuing individual contact with workers in field.
- (e) Provision, on a participating basis, for continuing economic security for professional workers.
- (f) Liberal attitude toward the investigator's work, his publication and reports.

To assist it in the fulfillment of its advisory functions the Committee, on its part, will make free use of either *ad hoc* or standing subcommittees in specific fields of interest. Furthermore, it proposes to arrange conferences of competent groups for discussion of problems, for interchange of reports, etc.; make surveys to analyze problems or to determine progress in areas of special interest pertaining to cancer; evaluate, through study by subcommittees and by the main committee, basic and clinical research undertakings, and submit recommendations for support to the American Cancer Society; initiate and plan broad or specific programs of basic and clinical research, through activities of the subcommittees and main committee, and secure the cooperative efforts of investigators in the general undertakings.

The Committee has established a central office in the Washington headquarters of the Council where information on all phases of cancer research will be assembled and from which reports may be distributed to interested investigators.

Many members of the Committee have participated intensively in the broad programs of research conducted under the pressure of war. It is both the hope and the sanguine expectation of the Committee that the fruitful pattern of cooperative investigations so successfully established during the war years, can now be carried on, modified and tempered to existing needs, into the continuing war against disease.

Membership of the Committee, as now constituted, includes the following:

Dr. C. P. Rhoads, *Chairman*  
 Dr. Florence R. Sabin, *Secretary*  
 Dr. A. R. Dochez  
 Dr. A. Baird Hastings  
 Dr. Charles B. Huggins  
 Dr. Donald F. Jones  
 Dr. C. C. Little  
 Dr. Carl R. Moore  
 Dr. John J. Morton  
 Dr. James B. Murphy  
 Dr. Eugene P. Pendergrass  
 Dr. Howard C. Taylor, Jr.  
 Dr. M. A. Tuve  
 Dr. M. C. Winternitz

PHILIP S. OWEN, M.D.,  
 For the Committee on Growth,  
 Division of Medical Sciences,  
 National Research Council,  
 2101 Constitution Avenue,  
 Washington 25, D. C.

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#### AN ABSTRACTING SERVICE FOR HUMAN BIOLOGY

The Trustees of *Biological Abstracts* announce the establishment, beginning in January, 1946, of a new section of *Biological Abstracts*—Section H, specially assembled Abstracts of Human Biology—intended for anthropologists, sociologists, psychologists, neurologists and psychiatrists, students of child development and human welfare, and students of man generally.

The new section will be an assemblage of all abstracts published in *Biological Abstracts* dealing with the broad field of human and social biology. Biological studies on human inheritance, on population and fertility, on endocrine and neurological factors affecting growth, development and human personality, on alcoholism and drug addiction, and on nervous disorders and mental deficiencies, and broad nutritional and epidemiological studies affecting human welfare, are some of the many fields that will be covered. The annual subscription price for the ten abstract issues, plus the complete index of the year's volume of *Biological Abstracts* will be \$6.00 (\$6.50 outside the United States).

Full information may be obtained by writing to Mr. H. I. Anderson, Business Manager, Biological Abstracts, University of Pennsylvania, Philadelphia 4, Pennsylvania.

The editors, Dr. Emil Novak and Dr. Nicholson G. Eastman, of Baltimore, announce the publication of a new abstract periodical, *Obstetrical and Gynecological Survey*. It will cover the entire medical periodical literature, both foreign and domestic, and will appear bimonthly beginning in February 1946. Nine hundred pages per year will be published and the subscription price will be \$9.00. The Williams & Wilkins Company, of Baltimore, will be the publishers.

### OBITUARIES

#### DR. WALTER BAUMGARTEN

Dr. Walter Baumgarten, F.A.C.P., of St. Louis, died at his summer home at Fish Creek, Wis., on August 23, 1945. A fire which destroyed his home caused his death.

His associates and his innumerable patients feel a great loss. Dr. Baumgarten for many years occupied a position of high importance in the field of Internal Medicine, and exerted a definite influence on the younger men who were associated with him in practice and at St. Luke's Hospital. He also made a deep impression by living up to a very high ideal of what the physician should be.

Born in St. Louis, October 31, 1873, it was natural for him to study Medicine, since his father was probably the outstanding Internist of his day in the Middle West, and one of the original members of the Association of American Physicians.

Walter Baumgarten obtained his college degree at Johns Hopkins University, and his medical degree at Washington University, where he was graduated in 1896. He was Assistant in Physiology in Harvard Medical School 1897-98, and Johns Hopkins University, 1902-03. He then became associated with Washington University School of Medicine, and maintained this connection until his death. He was deeply interested in the affairs of St. Luke's Hospital, and was at one time Director of the Department of Medicine. He was also Assistant Visiting Physician at Barnes Hospital.

He was a member of the St. Louis Medical Society, St. Louis Society of Internal Medicine, Missouri State Medical Association, and the American

Medical Association. He was a Fellow of the American College of Physicians since 1920.

RALPH A. KINSELLA, M.D., F.A.C.P.,  
Governor for Missouri

#### DR. JOHN GOOLD HARVEY

Dr. John Goold Harvey, F.A.C.P., died May 24, 1945, at the Veterans Administration Hospital, Dearborn, Michigan, of a cerebral hemorrhage. He had been an invalid for the last two or three years of his life.

Dr. Harvey was born in Detroit in 1875. He attended Princeton University and graduated from the University of Michigan Medical School in 1902. He was at one time associated with the United States Public Health Service and served as a medical officer in the United States Navy during World War I. He was a member of the Wayne County Medical Society, the Michigan State Medical Society, American Medical Association, and Fellow of the American College of Physicians since 1920.

Dr. Harvey spent most of his active years of practice in Detroit. He was highly respected by the members of his profession and enjoyed a nice practice with a very fine type of people. During the last few years of his practice he was physically handicapped and in spite of a splendid courage eventually had to retire. His passing is a deep loss to his many friends and patients.

P. L. LEDWIDGE, M.D., F.A.C.P.,  
Governor for Michigan

#### DR. FRIEDRICH ALEXANDER HECKER

Dr. Friedrich Alexander Hecker, F.A.C.P., for many years Pathologist at St. Joseph's Hospital, Ottumwa, Iowa, died June 3, 1945, of coronary thrombosis.

Dr. Hecker was born March 29, 1879. He attended Kemper Military School, Boonville, Missouri. He received a B.S. degree in 1908, an M.A. degree in 1911, and an M.D. degree in 1913, all from the University of Kansas. He had previously received the degree of D.D.S. in 1903 at the University of Pennsylvania. He served during the Spanish War, the Philippine Insurrection, and World War I. He was a Charter Member of the American Society of Clinical Pathologists, Diplomate of the American Board of Internal Medicine, and he had been a Fellow of the American College of Physicians since 1930. Dr. Hecker also was a member of the Wapello County Medical Society, Iowa State Medical Society, Iowa Clinical Society, the American Medical Association and the Society of American Bacteriologists.

Dr. Hecker was an earnest, enthusiastic worker, an unusual technician,

and had a vigorous personality. He will be keenly missed by his many friends in the medical profession.

B. F. WOLVERTON, M.D., F.A.C.P.,  
Governor for Iowa

#### DR. RAYMOND LUFT

The death of Dr. Luft as the result of a coronary thrombosis while serving in the Navy has removed from the ranks of the profession of Rhode Island one of the most capable and promising of our young physicians.

He was born in Jersey City, New Jersey, in 1904, was graduated from Rhode Island State College in 1926, took up postgraduate studies at Brown University, and received his M.D. from McGill University in 1934. He served an internship at the Royal Victoria Hospital in Montreal and held a residency at the Massachusetts General Hospital.

Dr. Luft began practice in West Warwick, where he held a part-time position in public health work, and later moved his office to Providence. He became a member of the Kent County and Rhode Island Medical Societies, and in 1939 was made an Associate of the American College of Physicians. At the start of his practice he joined the staff of the Rhode Island and Charles V. Chapin Hospitals. He was particularly interested in diabetes and was active in the Diabetic Clinic at the Rhode Island Hospital. He was an internist of ability and his loss is keenly felt by his colleagues. This is particularly true of the writer, to whom Dr. Luft was intimately known since his early student days.

ALEX. M. BURGESS, M.D., F.A.C.P.,  
Governor for Rhode Island

#### DR. JOSEPH McFARLAND

Dr. Joseph McFarland, F.A.C.P., Philadelphia, died suddenly on September 22, 1945, at the age of 77. Born in Philadelphia, February 9, 1868, Dr. McFarland graduated from the University of Pennsylvania in 1889. After further study in Europe, he returned to take up the teaching of Pathology. From 1896 until 1916 he was Professor of Pathology and Bacteriology at the Medico-Chirurgical College of Philadelphia. From 1910 to 1914 he also held the chair of Pathology in the Woman's Medical College of Pennsylvania. In 1916 he returned to the University of Pennsylvania as Professor of Pathology. He held the rank of Major in the first World War. Tuberculosis, contracted during his service in the Army, forced him to be relatively inactive for several years. However, by 1920 he was again actively teaching as Professor of General Pathology in the Thomas A. Evans Institute of the University of Pennsylvania. He became Emeritus Professor of Pathology in the University of Pennsylvania in 1936 upon reaching the age of 68.

Dr. McFarland wrote voluminously, being the author of at least four textbooks. Two of these, "The Pathogenic Bacteria and Protozoa" and "Textbook of Pathology," went through numerous editions.

Dr. McFarland belonged to numerous societies and organizations. He had been a Fellow of the American College of Physicians since 1923.

His great zeal for teaching and his love of his profession are exemplified by his last years. Although "retired for age," in 1936, Dr. McFarland resumed active teaching in 1940 as Professor of General Pathology in Temple University School of Dentistry. Not many months before his death he made an extensive lecture tour to a number of Latin American medical centers, an experience that gave him much satisfaction.

Active until the very end, he died as he would have wished, suddenly. His life was long and full. He will be held in affectionate memory by the many students who sat under him.

THOMAS M. McMILLAN, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania

#### DR. BENJAMIN A. SHEPARD

Dr. Benjamin A. Shepard, F.A.C.P., died June 16, 1945, at his residence in Kalamazoo, Michigan.

Dr. Shepard was born near Hillsdale, Michigan, July 13, 1879, and grew up in that community. He married Lola E. Hughes of Coldwater in 1900, just before entering the Detroit College of Medicine and Surgery. He was graduated from this institution, 1904, and practiced in Plainwell, Michigan, from 1904 to 1911. In that year he moved to Kalamazoo, Michigan, and became chief of staff of a small dispensary in 1912. Later he was the founder, owner and medical director of Pine Crest Sanatorium which was established in 1920. He was head of this fine institution for the treatment of tuberculosis, and especially interested in that field.

He was a past president of the Michigan State Tuberculosis Society, a member of the Board of Directors of the National Tuberculosis Association, and honorary president of the Kalamazoo Tuberculosis Association. He was a Fellow of the American College of Physicians, the American Medical Association, the American College of Chest Physicians, and past president and secretary of the Kalamazoo Academy of Medicine.

His passing is a distant loss to Kalamazoo and its surrounding territory.

P. L. LEDWIDGE, M.D., F.A.C.P.,  
Governor for Michigan